04-04-12

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	U.S. Patent 5,886,035
Issued:	December 18, 2017
To:	Ellchi Shirasawa, Masaaki Kageyama, Tadashi Nakajima, Takashi Nakano, Nobuaki Mori, Hideshi Sasakura, Yasushi Matsumura, Yoshitomi Moriziwa
Assignee:	Asahi Glass Company Ltd and Santen Pharmaceutical Co.,
For:	DIFLUOROPROSTAGLANDIN DERIVATIVES AND THEIR USE

Assistant Commissioner for Patents
Box Patent Extensions
Washington, D.C. 20231

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

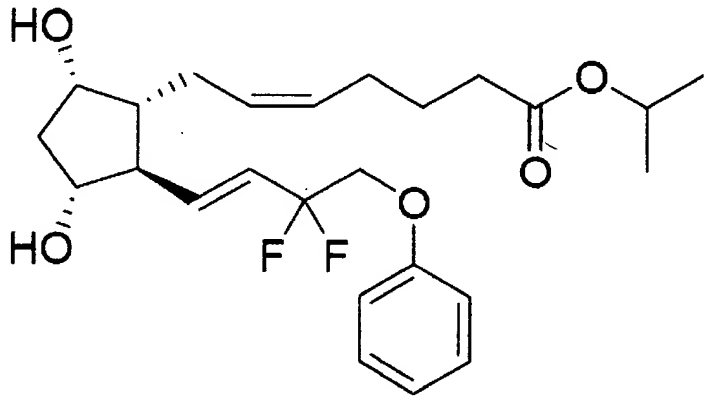
Sir:

Your Applicants, Asahi Glass Company Ltd., a company organized and existing under the laws of Japan and Santen Pharmaceutical Co., Ltd. represent that they are an assignee of the entire interest in and to Letters Patent of the United States 5,886,035 granted to Eiichi Shirasawa, Masaaki Kageyama, Tadashi Nakajima, Takashi Nakano, Nobuaki Mori, Hideshi Sasakura, Yasushi Matsumura, and Yoshitomi Moriziwa on the 23rd day of March, 1999 for DIFLUOROPROSTAGLANDIN DERIVATIVES AND THEIR USE by virtue of an assignment in favor of Asahi Glass Company Ltd., and Santen Pharmaceutical Co., Ltd., recorded December 18, 1997, Reel 008954, Frame 0860 (Attachment F). By the Power of Attorney enclosed herein (Attachments A1 and A2), Applicant appoints Merck & Co., Inc., a corporation organized and existing under the laws of the State of New Jersey and the exclusive licensee of the entire interest in and to Letters Patent of the United States 5,886,035, as its agent to act in its interest in this

matter. Applicant also appoints William Krovatin, Gerard Devlin and Sylvia A. Ayler as attorneys of Asahi Glass Company Ltd. and Santen Pharmaceutical Co., Ltd. with regard to this application for extension of term of U.S. Patent 5,886,035 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Applicant hereby submits this application for extension of patent term under 35 U.S.C. §156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. 1.740). For the convenience of the Patent and Trademark Office, the information contained in this application will be presented in a format which will follow the requirements of Section 1.740 of Title 37 of the Code of Federal Regulations.

(1) The approved product ZIOPTAN™ contains as the active ingredient, tafluprost, chemically described as 1-methylethyl (5*Z*)-7-{(1*R*, 2*R*, 3*R*, 5*S*)-2-[(1*E*)-3,3-difluoro-4-phenoxy-1-butenyl}-3,5-dihydroxycyclopentyl]-5-heptenoate. Its structural formula is:



(2) The approved product was subject to regulatory review under Section 505 of the Federal Food, Drug and Cosmetic Act Section 505 (21 U.S.C. §355).

(3) The approved product ZIOPTAN™ (tafluprost ophthalmic solution) received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act on February 10, 2012 (Attachment G).

(4) The only active ingredient in ZIOPTAN™ is tafluprost, which has not been approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA 202514 by the Food and Drug Administration on February 10, 2012.

(5) This Application for extension of patent term under 35 U.S.C. 156 is being submitted within the permitted 60 day period pursuant to 37 C.F.R. 1.720(f), said period which will expire on April 10, 2012.

(6) The complete identification of the patent for which extension is being sought is as follows:
Inventors: Eiichi Shirasawa, Masaaki Kageyama, Tadashi Nakajima, Takashi Nakano, Nobuaki Mori, Hideshi Sasakura, Yasushi Matsumura, and Yoshitomi Moriziwa
Patent Number: 5,886,035
Issue Date: March 23, 1999
Expiration Date: December 18, 2017 (20 years from the filing date).

(7) See "Attachment B" for a complete copy of the patent identified in paragraph (6) hereof.

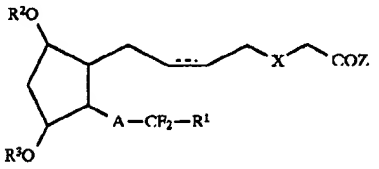
(8) No terminal disclaimer nor any certificate of Correction or Re-examination Certificate has been issued with regard to U.S. Patent No. 5,886,035. The Maintenance Fee Statement for U.S. Patent 5,886,035 is attached hereto as "Attachment C".

(9) U.S. Patent 5,886,035 claims the approved product. Specifically, the active ingredient, tafluprost, is claimed in Claims 1, 2, and 3; the pharmaceutical composition containing tafluprost is claimed in Claims 4 and 12, and the method of treatment of elevated intraocular pressure and ocular hypertension using tafluprost is claimed in Claims 5, 6, 7, 8, 9, 10, 11, 13, and 14.

Claims 1 through 14 read as follows:

What is claimed is:

1. A fluorine-containing prostaglandin derivative of the following formula (1) or a salt thereof:



(1)

wherein A is an ethylene group, a vinylene group, an ethynylene group, —OCH_2— or —SCH_2—,

R^1 is a substituted or unsubstituted aryloxyalkyl group,

each of R^2 and R^3 which are independent of each other, is a hydrogen atom or an acyl group, or forms a single bond together with Z,

X is —CH_2—, —O— or —S—,

Z is —OR^4, —$NHCOR^5$, —$NHSO_2R^6$ or —SR^7, or forms a single bond together with R^2 or R^3,

each of R^4, R^5, R^6 and R^7 which are independent of one another, is a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an aryl group or an aralkyl group,

and a dual line consisting of solid and broken lines is a single bond, a cis-double bond or a trans-double bond.

2. The compound according to claim 1, wherein R^1 is a phenoxymethyl group, a 3,5-dichlorophenoxymethyl group or a 3-chlorophenoxymethyl group.

3. The compound according to claim 1, which is 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ or an alkyl ester or a salt thereof.

4. A medicine containing the compound according to claim 1 as an active ingredient.

5. The medicine according to claim 4, which is a preventive or therapeutic medicine for an eye disease.

6. The medicine according to claim 5, wherein the eye disease is glaucoma or ocular hypertension.

7. The medicine according to claim 4, 5 or 6, wherein A is an ethylene group or a vinylene group.

8. The medicine according to claim 4, 5 or 6, wherein X is —CH_2—.

9. The medicine according to claim 4, 5 or 6, wherein both R^2 and R^3 are hydrogen atoms.

10. The medicine according to claim 4, 5 or 6, wherein Z is —OR^4.

11. The medicine according to claim 9, wherein R^1 is a phenoxymethyl group, a 3,5-dichlorophenoxymethyl group or a 3-chlorophenoxymethyl group.

12. A medicine containing 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ or an alkyl ester or salt thereof as an active ingredient.

13. The medicine according to claim 12, which is a preventive or therapeutic medicine for an eye disease.

14. The medicine according to claim 13, wherein the eye disease is glaucoma or ocular hypertension.

* * * * *

The approved product contains tafluprost which is a compound of Claim 1 wherein R^1 is unsubstituted aryloxyalkyl; R^2, and R^3, are hydrogen; R^4 is an alkyl group; Z is OR^4; X is –CH_2-l; and A is ethylene.

The product ZIOPTAN™ (tafluprost) has been approved under NDA 202514 as an ophthalmic solution for use in patients with open-angle glaucoma or ocular hypertension as described in more detail in the approved label. The active ingredient, tafluprost, is specifically claimed in claim 3.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) Investigational New Drug Application (IND 62690) for tafluprost ophthalmic soluction was filed on May 23, 2001 and became effective on June 24, 2001;

(ii) New Drug Application (NDA 202514) for ZIOPTAN™ (tafluprost ophthalmic soluction) was submitted on January 7, 2011; and

(iii) New Drug Application (NDA 202514) for ZIOPTAN™ (tafluprost ophthalmic soluction) was approved on February 10 2012.

(11) As a brief description of the activities undertaken by Applicant, Merck & Co., Inc., (exclusive licensee) and Santen Pharmaceutical Co., (licensor) during the applicable regulatory review period, attached hereto as "Attachment D" is a chronology of the major communications between the Applicant or licensor and the FDA from May 23, 2001 to February 10, 2012. Additionally, Applicant conducted three Phase 3 studies, 74460, 15-003, and 74458 and completed final study reports for each on March 29, 2006 (12 weeks report), August 20, 2007 (12 months report), and April 10, 2008 (24 months report), respectively. Protocol synopsis for 74458 was submitted along with 15-003 synopsis on September 16 2005. In April 2008 Applicants initiated discussions and actively negotiated an agreement with Merck & Co., Inc., which was executed on April 10, 2009. Merck assumed responsibility for seeking regulatory approval of the drug in the U.S.

(12)(A) Applicant is of the opinion that U.S. Patent 5,886,035 is eligible for extension under 35 U.S.C. §156 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C §156(a) -- U.S. Patent 5,886,035 claims the product, ZIOPTAN™ (tafluprost), the pharmaceutical composition of ZIOPTAN™ (tafluprost), and the method of using the ZIOPTAN™ (tafluprost) for treating glaucoma or ocular hypertension.

(b) 35 U.S.C §156(a)(1) -- The term of U.S. Patent 5,886,035 has not expired before submission of this application.

(c) 35 U.S.C §156(a)(2) -- The term of U.S. Patent 5,886,035 has never been extended.

(d) 35 U.S.C §156(a)(3) -- The application for extension is submitted by Applicant's agent, acting on behalf of the Applicant, who is the exclusive licensee of the patent, in accordance with the requirement of paragraphs (1) through (4) of 35 U.S.C §156(d) and rules of the Patent and Trademark Office.

(e) 35 U.S.C §156(a)(4) -- The product, ZIOPTAN™ (tafluprost), has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C §156(a)(5)(A) -- The commercial marketing or use of the product, ZIOPTAN™ (tafluprost), after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355) under which such regulatory review period occurred.

(g) 35 U.S.C §156(c)(4) -- No other patent has been extended for the same regulatory review period for the product, ZIOPTAN™ (tafluprost).

(12)(B) The length of extension of the patent term of U.S. Patent 5,886,035 claimed by Applicant is 1826 days or approximately 5 years. The length of the extension was determined pursuant to 37 C.F.R. §1.775 as follows:

(a) The regulatory review period under 35 U.S.C. §156(g)(1)(B) began on June 24, 2001 and ended on February 10, 2012 which is a total of 3,884 days or 10.63 years which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. §156(g)(2)(B)(i), the "Testing Period" began on June 24, 2001 and ended on January 7, 2011, which is 3,485 days or 9.54 years;

(ii) The period of review under 35 U.S.C. §156(g)(2)(B)(ii), the "Application Period" began on January 7, 2011 and ended on February 10, 2012, which is 399 days or 1.09 years;

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in sub-paragraph (12)(B)(a) above (3,884 days) less

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (March 23, 1999), which is 0 days, and

(ii) The number of days which applicant did not act with due diligence, which is 0 days, and

(iii) One-half the number of days determined in sub-paragraph (12)(B)(a)(i) minus the number of days as determined in sub-paragraph 12(B)(b)(i) after the patent issued ((3,485 – 0)/2) or 1742 days;

(iv) The regulatory period is calculated by subtracting the number of days determined in sub-paragraph (12)(B)(b)(i) – (iii) from the entire regulatory review period as determined in sub-paragraph (12)(B)(a) (which is 3,884 days-0 days-0 days-1742 days) which equals 2,142 days;

(c) The number of days as determined in sub-paragraph (12)(B)(b)(iv) (2,142 days) when added to the original term of the patent (December 18, 2017) would result in the date, October 30, 2023;

(d) Fourteen (14) years when added to the date of NDA approval (February 10, 2012) would result in the date, February 10, 2026;

(e) The earlier date as determined in sub-paragraph (12)(B)(c) and (12)(B)(d) is October 30, 2023;

(f) Since U.S. Patent 5,886,035 issued after September 24, 1984, the period of extension may not exceed five (5) years. Five (5) years when added to the original expiration date of the patent (December 18, 2017) would result in the date December 18, 2022, which is 1826 days and the length of extension being claimed;

(g) The earlier date as determined in sub-paragraph (12)(B)(e) and (12)(B)(f) is December 18, 2022.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee as set forth in 37 C.F.R. 1.20(j)(1) for receiving and acting upon this application is to be charged to the Deposit Account of Merck & Co., Inc., as authorized in the attached letter (Attachment E), which is submitted in duplicate.

(15) All correspondence and inquiries may be directed to the undersigned, whose address and telephone number are given below.

(16) The instant application for extension of patent term with regard to U.S. Patent No. 5,886,035 is being submitted as one original and triplicate copies thereof.

(17) The requisite declaration pursuant to 37 C.F.R. 1.740(b) is attached hereto.

Respectfully submitted,

By: Sylvia A. Ayler
Reg. No. 36,436
Attorney for Applicants
Merck & Co., Inc.
IP Group
P.O. Box 2000
Rahway, NJ 07065-0907
Telephone: (732) 594-4909
Facsimile: (732) 594-4720

Date: April 3, 2012

Attachments:
"Attachment A1" – Authorization of Agent and Power of Attorney
"Attachment A2" – Authorization of Agent and Power of Attorney
"Attachment B" – U.S. Patent 5,886,035
"Attachment C" – Copy of Receipt for Maintenance Fee Payment
"Attachment D" – Chronology of Major Communications with the FDA
"Attachment E" – Fee Transmittal
"Attachment F" – Copy of Assignment Abstract for U.S. Patent No. 5,886,035
"Attachment G" – Copy of FDA Approval for ZIOPTAN (tafluprost) with product circular

CERTIFICATION

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. 156 including its attachments and supporting papers is being submitted as one original and triplicate copies thereof.

By: Sylvia A. Ayler
Reg. No. 36,436
Attorney for Applicants
Merck & Co., Inc.
IP Group
P.O. Box 2000
Rahway, NJ 07065-0907
Telephone: (732) 594-4909
Facsimile: (732) 594-4720

Date: April 3, 2012

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	U.S. Patent 5,886,035
Issued:	December 18, 2017
To:	Ellchi Shirasawa, Masaaki Kageyama, Tadashi Nakajima, Takashi Nakano, Nobuaki Mori, Hideshi Sasakura, Yasushi Matsumura, Yoshitomi Moriziwa
Assignee:	Asahi Glass Company Ltd and Santen Pharmaceutical Co.,
For:	DIFLUOROPROSTAGLANDIN DERIVATIVES AND THEIR USE

Assistant Commissioner for Patents
Box Patent Extensions
Washington, D.C. 20231

Transmittal Letter for Application for Extension of Patent Term Under 35 U.S.C. §156

Dear Sir:

Transmitted herewith is the application of Merck Sharp & Dohme Corp., dated April 3, 2012 for extension of the term of United States Patent No. 5,886,035 under 35 U.S.C. §156, together with a duplicate of the papers thereof, certified as such.

Please charge the sum of $1,120.00 to Deposit Account 13-2755. Please also charge any additional fees which may be required by the filing of this application for Extension of Patent Term, or credit any overpayment to Deposit Account No. 13-2755. Two copies of this paper are enclosed.

By _____
Sylvia A. Ayler, Reg. No. 36,436
Attorney for Applicants
Merck Sharp & Dohme Corp.
P.O. Box 2000, Rahway, NJ 07065
(732)594-4909

~~04/04/2012 CCHAU1 00000039 132755 5886035~~
~~01 FC:1457 1120.00 DA~~

Date: April 3, 2012

Attachments:
"Attachment A1" – Authorization of Agent and Power of Attorney
"Attachment A2" – Authorization of Agent and Power of Attorney
"Attachment B" – U.S. Patent 5,886,035
"Attachment C" – Copy of Receipt for Maintenance Fee Payment
"Attachment D" – Chronology of Major Communications with the FDA
"Attachment E" – Fee Transmittal
"Attachment F" – Copy of Assignment Abstract for U.S. Patent No. 5,886,035
"Attachment G" – Copy of FDA Approval for ZIOPTAN (tafluprost) with product circular

CERTIFICATION

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. 156 including its attachments and supporting papers is being submitted as one original and triplicate copies thereof.

By: Sylvia A. Ayler
Reg. No. 36,436
Attorney for Applicants
Merck & Co., Inc.
IP Group
P.O. Box 2000
Rahway, NJ 07065-0907
Telephone: (732) 594-4909
Facsimile: (732) 594-4720

Date: April 3, 2012

Attachment A1

PTR Application
ZIOPTAN

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	U.S. Patent 5,886,035
Issued:	March 23, 1999
To:	Eiichi Shirasawa, Masaaki Kageyama, Tadashi Nakajima, Takashi Nakano, Nobuaki Mori, Hideshi Sasakura, Yasushi Matsumura, Yoshitomi Morizawa
Assignee:	Asahi Glass Company, Limited and Santen Pharmaceutical Co.,Ltd.
For:	DIFLUOROPROSTAGLANDIN DERIVATIVES AND THEIR USE

Assistant Commissioner for Patents
Box Patent Extensions
Washington, D.C. 20231

AUTHORIZATION OF AGENT AND POWER OF ATTORNEY

I, Masamichi Sato do hereby declare:

Santen Pharmaceutical Co.,Ltd., a company organized and existing under the laws of the Japan, and having its registered office at 9-19, Shimoshinjo 3-Chome, Higashiyodogawa-ku, Osaka 533-8651 Japan, being an owner of record of the above-identified U.S. Letters Patent, hereby authorize and appoint, Merck & Co., Inc., a corporation organized and existing under the laws of New Jersey and having its head office at One Merck Drive, P.O. Box 100, Whitehouse Station, New Jersey 08889-0100, and the Patent Attorneys named below:

William Krovatin	(Reg. No. 33,256)
Gerard Devlin	(Reg. No. 43,586)
Sylvia A. Ayler	(Reg. No. 36,436)

all being employees of Merck & Co., Inc., individually and collectively to be the agents and attorneys of Santen Pharmaceutical Co.Ltd., with regard to an application for extension of the term of U.S. Patent 5,886,035 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Please address all communications in the above matter to:

Sylvia A. Ayler
Assistant Counsel
Merck & Co., Inc.
126 E. Lincoln Avenue
Rahway, New Jersey 07065-0907

Santen Pharmaceutical Co.,Ltd.
By Masamichi Sato
Name: Masamichi Sato
Title: Corporate Officer
Head of Corporate Development Division

Date:

Attachment A2

PTR Application
ZIOPTAN

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	U.S. Patent 5,886,035
Issued:	March 23, 1999
To:	Eiichi Shirasawa, Masaaki Kageyama, Tadashi Nakajima, Takashi Nakano, Nobuaki Mori, Hideshi Sasakura, Yasushi Matsumura, Yoshitomi Morizawa
Assignee:	Asahi Glass Company, Limited and Santen Pharmaceutical Co., Ltd.
For:	DIFLUOROPROSTAGLANDIN DERIVATIVES AND THEIR USE

Assistant Commissioner for Patents
Box Patent Extensions
Washington, D.C. 20231

AUTHORIZATION OF AGENT AND POWER OF ATTORNEY

I, [**Kazuhiko Saito**] do hereby declare:

Asahi Glass Company, Limited, a company organized and existing under the laws of the Japan, and having its registered office at 5-1, Marunouchi 1-chome, Chiyoda-ku, Tokyo 100-8405 Japan, being an owner of record of the above-identified U.S. Letters Patent, hereby authorize and appoint, Merck & Co., Inc., a corporation organized and existing under the laws of New Jersey and having its head office at One Merck Drive, P.O. Box 100, Whitehouse Station, New Jersey 08889-0100, and the Patent Attorneys named below:

William Krovatin	(Reg. No. 33,256)
Gerard Devlin	(Reg. No. 43,586)
Sylvia A. Ayler	(Reg. No. 36,436)

all being employees of Merck & Co., Inc., individually and collectively to be the agents and attorneys of Asahi Glass Company, Limited, with regard to an application for extension of the term of U.S. Patent 5,886,035 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Please address all communications in the above matter to:

Sylvia A. Ayler
Assistant Counsel
Merck & Co., Inc.
126 E. Lincoln Avenue
Rahway, New Jersey 07065-0907

Asahi Glass Company, Limited

By Kazuhiko Saito

Name: Kazuhiko Saito
Title: General Manager, Intellectual Property Center

Date: February 29, 2012

US005886035A

United States Patent [19]

Shirasawa et al.

[11] Patent Number: 5,886,035

[45] Date of Patent: Mar. 23, 1999

[54] **DIFLUOROPROSTAGLANDIN DERIVATIVES AND THEIR USE**

[75] Inventors: **Eiichi Shirasawa**; **Masaaki Kageyama**; **Tadashi Nakajima**, all of Ikoma; **Takashi Nakano**, Yokohama; **Nobuaki Mori**, Yokohama; **Hideshi Sasakura**, Yokohama; **Yasushi Matsumura**, Yokohama; **Yoshitomi Morizawa**, Yokohama, all of Japan

[73] Assignees: **Asahi Glass Company Ltd.**, Tokyo, Japan; **Santen Pharmaceutical Co., Ltd.**, Osaka, Japan

[21] Appl. No.: **993,017**

[22] Filed: **Dec. 18, 1997**

[30] **Foreign Application Priority Data**

Dec. 26, 1996 [JP] Japan 8-348614
Mar. 26, 1997 [JP] Japan 9-074054
Jun. 27, 1997 [JP] Japan 9-172477

[51] **Int. Cl.**[6] **C07C 405/00**; A61K 31/557

[52] **U.S. Cl.** **514/330**; 514/573; 510/121; 562/503

[58] **Field of Search** 560/121; 502/503; 514/530, 573

[56] **References Cited**

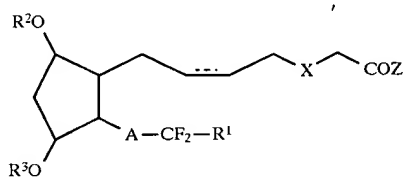
U.S. PATENT DOCUMENTS

5,166,178 11/1992 Ueno 514/573

Primary Examiner—Robert Gerstl
Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

[57] **ABSTRACT**

A fluorine-containing prostaglandin derivative of the formula (1) (or a salt thereof) and a medicine containing it, particularly, a preventive or therapeutic medicine for an eye disease:



(1)

wherein A is a vinylene group or the like, R^1 is an aryloxyalkyl group or the like, R^2 and R^3 are hydrogen atoms or the like, and Z is OR^4 (wherein OR^4 is a hydrogen atom or an alkyl group) or the like.

14 Claims, No Drawings

DIFLUOROPROSTAGLANDIN DERIVATIVES AND THEIR USE

The present invention relates to fluorine-containing prostaglandin derivatives having two fluorine atoms at the 15-position (or their salts) and medicines containing the compounds as an active ingredient, particularly, preventive or therapeutic medicines for eye diseases.

The naturally occurring prostaglandins (PGs) are a class of biologically active substances synthesized in the body and cellular functions in various tissues of the body as local hormones having various biological activities. The PGs F, a group of naturally occurring PGs, are known to lower intraocular pressure when topically applied to the eye and are expected to find applications as therapeutic medicines for ocular hypertension or glaucoma (U.S. Pat. No. 4,599, 353). However, they are irritant to the eye and have a problem of their inflammatory side effects such as congestion and damage to the cornea. Therefore, research for development of PGF derivatives which do not have such side effects is extensively conducted both at home and abroad. PGF derivatives having a cyclic structure in the ω-chain are also known. Shielnshantz et al. reported specific PGA, PGB, PGD, PGE and PGF derivatives modified by introduction of a cyclic structure are less irritant and congestive to the eye (Japanese Unexamined Patent Publication JP-A-8-109132). Ophthalmic compositions for local therapeutic medicines for glaucoma and ocular hypertension containing a chloprostenol or fluprostenol analog have been also reported (Japanese Unexamined Patent Publication JP-A-7-165703).

Among the above-mentioned compounds disclosed in the literature, the compound 13,14-dihydro-17-phenyl-18, 19,20-trinor-$PGF_{2\alpha}$ isopropyl ester (Latanoprost) has an excellent pharmacological effect, and ophthalmic solutions containing Latanoprost as an active ingredient are used for treatment of glaucoma and ocular hypertension at actual medical sites. Although Latanoprost is less irritant and congestive to the eye, there is still room for improvement in the melanogenesis-stimulating property and the duration of efficacy. In particular, Latanoprost stimulates melanogenesis, and its side effect of causing iridal pigmentation (A. Alm, et al, Ophthalmology, Vol. 102, No. 12, 1743–1752 (1995)) remains a problem to be solve.

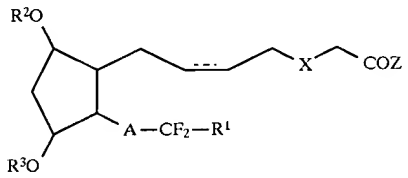
For this reason, extensive research has been conducted both at home and abroad for development of long-lasting PGF derivatives having much the same biological activities as the naturally occurring one and few side effects.

Meanwhile, Bezglov et al. reported 15-fluoro-15-deoxy $PGF_{2\alpha}$, which is derived from naturally occurring PGF2α by introducing fluorine at the 15-position and retains the skeleton of its origin. 15-Fluoro-15-deoxy-$PGF_{2\alpha}$ is reported to have remarkable pharmacological actions such as the 100-fold greater contraction action and the 1000-fold relaxation action on smooth muscle in the respiratory system as compared with those of the naturally occurring $PGF_{2\alpha}$ and the action on the smooth muscle in the digestive and circulatory systems comparable to that of the naturally occurring $PGF_{2\alpha}$ (Izv. Akad. Nauk SSSR, Ser. Biol., 6,831 (1989)). However, no report has been made on any pharmacological actions of the compound on any eye disease, particularly on glaucoma.

No prostaglandin F derivatives that have a fluorine atom at the 15-position have been known except 15-fluoro-15-deoxy-$PGF_{2\alpha}$. Especially, no report has been made on derivatives having two fluorine atoms at the 15-position, 15,15-difluoro-15-deoxy PGs $F_{2\alpha}$ per se or their synthesis.

The present inventors synthesized 15,15-difluoro-15-deoxy-$PGF_{2\alpha}$ and its novel derivatives and measured their biological activities to assess their usefulness as medicines. The present inventors also measured the biological activities of derivatives of 15,15-difluoro-15-deoxy-$PGF_{2\alpha}$ which have a substituted or unsubstituted aryloxy group on the ω-chain and are prepared by modifying the carboxyl group or the hydroxyl group of the prostaglandin to assess their usefulness as medicines. As a result, the present inventors have found that 15,15-difluoro-15-deoxy-$PGF_{2\alpha}$ and its derivatives are superior to the known natural $PGF_{2\alpha}$ in the effect of lowering intraocular pressure are scarcely irritant to the eye, scarcely affect the ocular tissues such as the cornea, the iris and the conjunctive, and have long-lasting efficacy. They are characterized in that they stimulates melanogenesis much less as well as in that their efficacy lasts longer than Latanoprost.

The present invention relates to the compound 15,15-difluoro-15-deoxy-$PGF_{2\alpha}$ and its derivatives and their use as medicines, in particular, as medicines for eye diseases, and provides a fluorine-containing prostaglandin derivative of the following formula (1) or a salt thereof:



(1)

wherein A is an ethylene group, a vinylene group, an ethynylene group, —OCH_2— or —SCH_2—,

R^1 is a substituted or unsubstituted C_{3-8} alkyl group, a substituted or unsubstituted C_{3-8} alkenyl group, a substituted or unsubstituted C_{3-8} alkynyl group, a substituted or unsubstituted C_{3-8} cycloalkyl group, a substituted or unsubstituted aralkyl group or a substituted or unsubstituted aryloxyalkyl group,

each of R^2 and R^3 which are independent of each other, is a hydrogen atom or an acyl group, or forms a single bond together with Z,

X is —CH_2—, —O— or —S—, Z is —OR^4, —$NHCOR^5$, —$NHSO_2R^6$ or —SR^7, or forms a single bond together with R^2 or R^3,

each of R^4, R^5, R^6 and R^7 which are independent of one another, is a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an aryl group or an aralkyl group,

and a dual line consisting of solid and broken lines is a single bond, a cis-double bond or a trans-double bond, a medicine containing the above compound as an active ingredient; and a preventive or therapeutic medicine for an eye disease containing the above compound as an active ingredient.

The fluorine-containing prostaglandin derivatives of the present invention may be the same as the naturally occurring type except for the two fluorine atoms at the 15-position (namely, compounds wherein A is a vinylene group, R^1 is a n-pentyl group, both R^2 and R^3 are hydrogen atoms, X is —CH_2—, Z is —OH, and the dual line is a cis-double bond). However, among the fluorine-prostaglandin derivatives of the present invention, those having an ω-chain which is not of the naturally occurring type (namely, wherein A is a vinylene group, and R^1 is a n-pentyl group) are preferred. In particular, those having wherein R^1 is one of the above-mentioned groups except an alkyl group are preferred.

In the present invention, the eye disease as the target for prevention or therapy is preferably glaucoma or ocular hypertension.

In the following description, the term "lower" for an organic group corresponds to a carbon number of from 1 to 6. A preferred lower organic group is an organic group having from 1 to 4 carbon atoms.

An "alkyl group" may be linear or branched, and unless otherwise noted, a lower alkyl group is preferred. Specific examples include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group, a t-butyl group, a pentyl group and a hexyl group.

An "alkenyl group" is preferably a lower alkenyl group, unless otherwise noted, and more preferably a linear or branched alkenyl group having from 2 to 6 carbon atoms and one unsaturated group. Specific examples include a vinyl group, an allyl group, a 1-propenyl group, an isopropenyl group, a 3-butenyl group, a 3-pentenyl group and a 4-hexenyl group.

An "alkynyl group" is preferably a lower alkynyl group, unless otherwise noted, more preferably a linear or branched alkynyl group having from 2 to 6 carbon atoms and one unsaturated group. Specific examples include a 1-propynyl group, a 2-propynyl group, a 3-butynyl group, a 3-pentynyl group and a 4-hexynyl group.

As an "alkoxy group", although a wide variety of common alkoxy groups may be used, a lower alkoxy group is preferred, and more preferred is a linear or branched alkoxy group having from 1 to 4 carbon atoms. Specific examples include a methoxy group, an ethoxy group, a propoxy group and a butoxy group.

A "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

An "aryl group" means a monovalent aromatic hydrocarbon group which may have a substituent (such as a lower alkyl group, a halogen atom, a haloalkyl group, a lower alkoxy group or a lower alkylamino group), preferably a phenyl group or its derivative. For example, a phenyl group, a tolyl group, a halophenyl group (such as a chlorophenyl group, a fluorophenyl group or a bromophenyl group), a dihalophenyl group (such as a dichlorophenyl group, a difluorophenyl group or a dibromophenyl group), a trihalophenyl group (such as a trichlorophenyl group, a trifluorophenyl group or a tribromophenyl group), a haloalkylphenyl group (such as a trifluoromethylphenyl group), an alkoxyphenyl group (such as a methoxyphenyl group or an ethoxyphenyl group), a dialkoxyphenyl group (such as a dimethoxyphenyl group or a diethoxyphenyl group) or a trialkoxyphenyl group (such as a trimethoxyphenyl group or a triethoxyphenyl group) may be mentioned.

An "aralkyl group" means an aryl-substituted alkyl group, in which the aryl group as the substituent may be as described above, and the carbon number of the alkyl group is preferably from 1 to 4. Specific examples include a benzyl group, a benzhydryl group, a trityl group and a phenethyl group.

A "cycloalkyl group" means an unsubstituted or substituted 3 to 8-membered cycloalkyl group, and when substituted, may have a lower alkyl group, a halogen atom or an alkoxy group as a substituent. For example, a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, a methylcyclohexyl group, a dimethylcyclopentyl group, a dimethylcyclohexyl group, a chlorocyclohexyl group or a dichlorocyclohexyl group may be mentioned.

A "haloalkyl group" means a lower haloalkyl group having at least one halogen atom. A fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a trifluoroethyl group, a pentafluoroethyl group, a chloromethyl group, a dichloromethyl group, a trichlromethyl group or a bromomethyl group may be mentioned.

An "acyl group" means a monovalent or polyvalent group derived from a carboxylic acid by removing hydroxyl group (s) from all the carboxyl group(s). As the carboxylic acid, a saturated or unsaturated aliphatic carboxylic acid, a carbocyclic carboxylic acid or a heterocyclic carboxylic acid may be mentioned. As the carbocyclic carboxylic acid, a saturated or unsaturated alicyclic carboxylic acid or an aromatic caroboxylic acid may be mentioned.

Among the fluorine-containing prostaglandin derivatives of the formula (1) (hereinafter referred to as the fluorine-containing prostaglandin derivatives (1)), the following compounds are preferred from the standpoint of biological activities and physical properties.

As A, a vinylene group or an ethylene group is preferred, and the vinylene group induces cis- or trans-vinylene groups. A trans-vinylene group is particularly preferred. In the case of —OCH_2— or —SCH_2—, the oxygen atom or the sulfur atom is preferably linked to the ring.

As X, —CH_2— is particularly preferred.

The dual line consisting of solid and broken lines is preferably a cis-double bond.

R^1 is preferably an organic group corresponding to the ω-chain moiety of the naturally occurring $PGF_{2\alpha}$ (when the rest is not of the naturally occurring type) or an organic group corresponding to the ω-chain moiety of any of various synthetic PGs $F_{2\alpha}$. Such organic groups include, for example, a C_{3-8} alkyl group, a C_{3-8} alkenyl group, a C_{3-8} alkynyl group, a C_{3-8} cycloalkyl group, an aralkyl group, an aryloxy group having an aryl group such as a phenyl group, and such groups having various substituents.

The alkyl group may have a cyclic organic group such as a cycloalkyl group as a substituent, and the alkenyl group and the alkynyl group may have a cyclic organic group such as an aryl group or a cycloalkyl group as a substituent. For example, R^1 may be a cycloalkyl group-substituted alkyl group, a cycloalkyl group-substituted alkenyl group, or an aryl group-substituted alkenyl group. Further, it may be an organic group having an oxygen atom or a sulfur atom introduced to replace a carbon atom of a linear organic group such as an alkyl group, or an organic group having a cyclic organic group such as a cycloalkylene group or an arylene group introduced between two carbon atoms of a linear organic group. Further, a cycloalkyl group, an aralkyl group, an aryloxy group and an organic group having such a group as a substituent may have a linear organic group such as an alkyl group as a substituent on the ring moiety. Substituents in R^1 include, in addition to the above-mentioned substituents, a halogen atom, an oxygen atom-containing substituent, a sulfur atom-containing substituent, a nitrogen atom-containing substituent, and others.

When R^1 is a linear substituted or unsubstituted group, a linear C_{5-6} alkyl group, a linear C_{5-6} alkenyl group and a linear C_{5-6} alkynyl group and such groups substituted with one or two methyl group are particularly preferred. Specific linear groups as R^1 include the following groups. Among them, preferred are a n-pentyl group, a 2-methylhexyl group, a 1-methyl-3-pentynyl group, a 1-methyl-3-hexynyl group, and a 1,1-dimethyl-3-hexynyl group.

A n-propyl group, a n-butyl group, a n-pentyl group, a n-hexyl group, a n-heptyl group, a n-octyl group, a n-decyl group, a 1-methylpentyl group, a 1,1-dimethylpentyl group, a 1-methylhexyl group, a 2-methylpentyl group, a 2-methylhexyl group, a 3-pentenyl group, a 1-methyl-3-pentenyl group, a 1-methyl-3-hexenyl group, a 1,1-dimethyl-3-pentenyl group, a 1,1-dimethyl-3-hexenyl

group, a 2-methyl-3-pentenyl group, a 2-methyl-3-hexenyl group, a 3-pentynyl group, a 1-methyl-3-pentynyl group, a 1-methyl-3-hexynyl group, a 2-methyl-3-pentynyl group, a 2-methyl-3-hexynyl group, a 1,1-dimethyl-3-pentynyl group, and a 1,1-dimethyl-3-hexynyl group.

The substituted or unsubstituted cycloalkyl group as R^1 is preferably a C_{3-8} cycloalkyl group, or such a cycloalkyl group substituted by at least one lower alkyl group. Particularly preferred is an unsubstituted cyclopentyl group, an unsubstituted cyclohexyl group, a C_{1-4} alkyl group-substituted cyclopentyl group, or a C_{1-4} alkyl group-substituted cyclohexyl group.

The substituted or unsubstituted aralkyl group as R^1 is preferably an aralkyl group which contains, for example, a benzene ring, a furan ring, a thiophene ring or a naphthalene ring and may be substituted by, for example, a halogen atom, a haloalkyl group, an alkoxy group or a hydroxyl group. The carbon number of the alkyl moiety (i.e. the alkylene group) of the aralkyl group is preferably from 1 to 4. A particularly preferred aralkyl group is a C_{1-2} alkyl group substituted with a phenyl group or a C_{1-2} alkyl group substituted with a phenyl group substituted with one or two lower alkyl groups.

Specifically, a phenylmethyl group, a 2-phenylethyl group, a 3-methylphenylmethyl group, a 2-(3-methylphenyl) ethyl group, a 3-trifluoromethylphenylmethyl group, a 2-(3-trifluoromethylphenyl)ethyl group, a 3-chlorophenylmethyl group, a 2-(3-chlorophenyl)ethyl group, a 2-(3,5-dichlorophenyl)ethyl group and a 2-(3,4-dichlorophenyl) ethyl group are preferred.

The substituted or unsubstituted aryloxyalkyl group as R^1 is preferably an aryloxyalkyl group which contains, for example, a benzene ring, a furan ring, a thiophene ring or a naphthalene ring and may have, for example, a halogen atom, a haloalkyl group, an alkoxy group or a hydroxyl group as a substituent on the aryl moiety. The aryl moiety is preferably a phenyl group which is not substituted or substituted with from 1 to 3 halogen atoms or haloalkyl groups. The carbon number of the alkyl moiety substituted with an aryloxy group is preferably from 1 to 3.

Specific preferred aryloxyalkyl groups as a phenoxymethyl group, a 3-chlorophenoxymethyl group, a 3-fluorophenoxymethyl group, a 3-trifluoromethylphenoxymethyl group, a 3,5-dichlorophenoxymethyl group, a 3,4-dichlorophenoxymethyl group, a 3,5-difluorophenoxymethyl group, a 3,4-difluorophenoxymethyl group, a 3,5-bis(trifluoromethyl)phenoxymethyl group and a 3,4-bis(trifluoromethyl)phenoxymethyl group.

As R^1, in addition to those described above, a C_{1-4} alkyl group substituted by the above-mentioned cycloalkyl group is preferred as a type of substituted alkyl group. As such a cycloalkyl group, a cyclopentyl group or a cyclohexyl group is preferred, and as such an alkyl group, a C_{1-2} alkyl group is preferred. Specific examples include a cyclopentylmethyl group, a 2-cyclopentylethyl group and a cyclohexylmethyl group.

As R^1, more preferred are the above-mentioned substituted or unsubstituted aryloxyalkyl groups. Among them, a substituted or unsubstituted phenoxymethyl group such as a phenoxymethyl group, a 3-chlorophenoxymethyl group, a 3,5-dichlorophenoxymethyl group or a 3,4-dichlorophenoxymethyl group is preferred.

Each of R^2 and R^3 which are independent of each other, is a hydrogen atom or an acyl group, or forms a single bond as described later. It is preferred that both R^2 and R^3 are hydrogen atoms, or that either R^2 or R^3 is an acyl group and the other is a hydrogen atom. When only one of them is an acyl group, it is preferred that R^2 is an acyl group. Compounds wherein at least one of R^2 and R^3 is an acyl group are useful as prodrugs because they hydrolyze in vivo to biologically active compounds. As the acyl group, a C_{2-20} acyl group, particularly, an aliphatic hydrocarbon type C_{2-20} acyl group is preferred. In particular, fluorine-containing prostaglandin derivatives wherein either R^2 or R^3 is an aliphatic linear hydrocarbon type acyl group having a carbon number of at least 4 are useful as prodrugs having improved lipid solubility.

Z is $—OR^4$, $—NHCOR^5$, $—NHSO_2R^6$, $—SR^7$ or represents a single bond together with R^2 or R^3, which means cyclization of a compound wherein Z is OH and either R^2 or R^3 is a hydrogen atom (a compound having a carboxyl group at the end of the α-chain and a hydroxyl group either at the 9-position or at the 11-position) by esterification of the carboxyl group and the hydroxyl group to form an ester bond between the end of the α-chain and the 9- or 11-position. Such cyclic compounds having an ester bond hydrolyze in vivo into biologically active compounds, and therefore are useful as prodrugs.

As R^4–R^7 in the groups represented by $—OR^4$, $—NHCOR^5$, $—NHSO_2R^6$ and $—SR^7$, a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an aryl group and an aralkyl group may be mentioned. The alkyl group, the alkenyl group, the alkynyl group and the alkyl moiety of the aralkyl group may be linear or branched and may have various substituents such as halogen atoms. The cycloalkyl group, the aryl group and the aralkyl group may have an alkyl group or other substituents on the ring. As such substituents, the substituents described above for R^1 may be mentioned.

The alkyl group, the alkenyl group and the alkynyl group as R^4–R^7 preferably have a carbon number of at most 20, particularly, at most 8. Specific examples of these linear hydrocarbon groups include the following groups. As the alkyl group, a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, a n-pentyl group, a n-hexyl group, a n-heptyl group, a n-octyl group, a n-decyl group, a 1-methylpentyl group, a 1,1-dimethylpentyl group, a 1-methylhexyl group, a 2-methylpentyl group and 2-methylhexyl group may be mentioned.

As the alkenyl group, an allyl group, a 2-butenyl group, a 3-pentenyl group, 1-methyl-3-pentenyl group, 1-methyl-3-hexenyl group, 1,1-dimethyl-3-pentenyl group and a 1,1-dimethyl-3-hexenyl group may be mentioned.

As the alkenyl group, a propargyl group, a 3-pentynyl group, a 1-methyl-3-pentynyl group, a 1-methyl-3-hexynyl group, a 1,1-dimethyl-3-pentynyl group and a 1,1-dimethyl-3-hexynyl group may be mentioned.

As the substituted alkyl group, a halogen atom-substituted alkyl group or a cycloalkyl group-substituted alkyl group may be mentioned. The carbon number of the halogen atom-substituted alkyl group is preferably at most 6, and the carbon number of the alkyl moiety of the cycloalkyl group-substituted alkyl group is preferably from 1 to 2. As the halogen atom-substituted alkyl group, for example, a trifluoromethyl group or a pentafluoroethyl group may be mentioned. As the cycloalkyl group-substituted alkyl group, for example, a cyclobutylmethyl group, a cyclopentylmethyl group or a cyclohexylmethyl group may be mentioned.

The carbon number of the cycloalkyl group is preferably at most 10. Specific examples include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a 2,2-dimethylcyclopropyl group, a 3-cyclopentenyl group, a 3-cyclohexynyl group and a cyclooctanyl group.

As the aryl group, a substituted or unsubstituted phenyl group is preferred. As the substituent, an alkyl group

(preferably having a carbon number of at most 4), a halomethyl group, a halogen atom, an alkoxy group, an acyl group, an acylamino group or a nitro group is preferred. Specific examples of the aryl group include a phenyl group, a 4-methylphenyl group, a 4-(t-butyl)phenyl group, a 3-trifluoromethylphenyl group, a 4-trifluoromethylphenyl group, a 4-chlorophenyl group, a 4-acetylphenyl group, a 4-benzoylphenyl group, a 4-acetylaminophenyl group, a 4-benzoylaminophenyl group, a 3-nitrophenyl group and a 4-nitrophenyl group.

As the aralkyl group, an aralkyl group consisting of an alkyl moiety having a carbon number of at most 4 (preferably a carbon number of 1 or 2) and a phenyl group is preferred. The phenyl group may be substituted with an alkyl group (preferably having a carbon number of at most 4), a halomethyl group, a halogen atom, an alkoxy group, an acyl group, an acylamino group, a nitro group or the like. The alkyl moiety of the aralkyl group may be branched. Specific examples include:

a benzyl group, a phenethyl group, a diphenylmethyl group, a 3-methylphenylmethyl group, a 3-chlorophenylmethyl group, a 3-fluoromethylphenylmethyl group, a 3-bromophenylmethyl group, a 3-trifluoromethylphenylmethyl group, a 1-(3-methylphenyl)ethyl group, a 1-(3-chlorophenyl)ethyl group, a 1-(3-trifluoromethylphenyl)ethyl group, a 1-(3-fluorophenyl)ethyl group, a 1-(3-bromophenyl) ethyl group, a 2-(3-methylphenyl)ethyl group, a 2-(3-chlorophenyl)ethyl group, a 2-(3-trifluoromethylphenyl)ethyl group, a 2-(3-fluorophenyl)ethyl group, a 2-(3-bromophenyl)ethyl group, a 1-methyl-2-(3-methylphenyl)ethyl group, a 1-methyl-2-(3-chlorophenyl)ethyl group, a 1-methyl-2-(3-trifluoromethylphenyl)ethyl group, a 1-methyl-2-(3-fluorophenyl)ethyl group and a 1-methyl-2-(3-bromophenyl)ethyl group.

Each of R^4–R^7 is preferably a substituted or unsubstituted alkyl, cycloalkyl or aralkyl group. As the substituent, a halogen atom or an alkyl group having a carbon number of at most 4 which is bonded to a ring is preferred. Particularly preferred R^4–R^7 are alkyl groups, and a haloalkyl is particularly preferred as R^6.

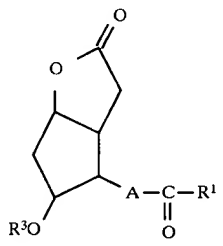
Z is preferably a group represented by —OR^4. R^4 in Z is preferably a hydrogen atom or a C_{1-20} hydrocarbon group such as an alkyl group, a cycloalkyl group or an aralkyl group. Compounds wherein R^4 is a hydrocarbon group are useful as prodrugs because they hydrolyze in vivo into biologically active compounds. It is possible to improve the lipid solubility of compounds by proper selection of hydrocarbon groups. As Z, particularly preferred are a hydroxyl group, a methoxy group, an ethoxy group, an isopropoxy group, an isobutoxy group, a cyclohexyloxy group and a benzyloxy group.

A fluorine-containing prostaglandin derivative of the present invention having an acidic group such as a carboxy group, for example like those wherein Z is a hydroxyl group, may take the form of a salt with a base. Similarly, when a compound of the present invention has a basic group such as an amino group, it may take the form of a salt with an acid. Salts with bases include alkali metal salts such as sodium salts and potassium salts, alkaline earth metal salts such as calcium salts and magnesium salts and ammonium salts such as unsubstituted ammonium salts and alkyl-substituted ammonium salts. Salts with acids include inorganic acid salts such as hydrochlorides, sulfates and phosphates and organic acid salts such as acetates, oxalates, citrates, succinates and p-toluenesulfonates.

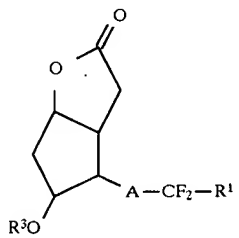
The fluorine-containing prostaglandin derivatives of the present invention can be synthesized by a process similar to a general process for producing prostaglandin $F_{2\alpha}$. For example, first of all, the ω-chain is introduced into the starting material, a Corey lactone, and the resulting enone is converted by fluorination into an ω-chain-containing Corey lactone having two fluorine atoms at the 15-position. Subsequent reduction of the lactone is to a lactol followed by introduction of the α-chain unit by the Wittig reaction, and, if necessary, acylation or of a hydroxyl group or removal of the protecting group for a hydroxyl group, gives fluorine-containing prostaglandin derivatives of the present invention. The introduction of the α-chain unit may be followed by conversion of a carboxyl group into an ester, an acyl amide, a sulfonamide or a thioester and, if necessary, removal of the protecting group for a hydroxyl group or acylation of a hydroxyl group to produce fluorine-containing prostaglandin derivatives of the present invention.

Specifically speaking, the fluorine-containing prostaglandin derivatives (1) can be prepared, for example, by a process comprising fluorination of a ketone (2) having an ω-chain to give an ω-chain-containing Corey lactone (3) having two fluorine atoms at the 15-position, reduction of the lactone (3) to a lactol (4) and reaction of the lactol (4) with a phosphorane (5) to introduce an α-chain unit. The phosphorane (5) is obtainable from a phosphonium salt (6). Because it is not necessary for the starting compound to have the same configuration as the resulting fluorine-containing prostaglandin derivative (1), the following formulae (2) to (4) do not specify the configurations of the substituents bonded to the cyclopentane rings. In the formulae (5) and (6), R^8 is a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group or a dialkylamino group, and Y is a halogen atom such as a chlorine atom, a bromine atom or an iodine atom.

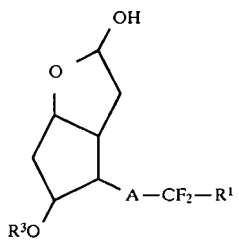
(2)



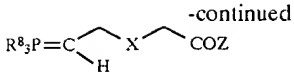
(3)



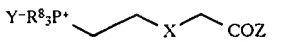
(4)



-continued



(5)



(6)

The ketones shown above are known compound except those having specific substituents as R^1. The novel ketones having specific substituents as R^1 can be prepared by a process similar to that for the other known ketones. For example, these ketones can be prepared by reaction of a dialkyl 3-substituted-2-oxopropylphosphonate with a Corey lactone having a formyl group.

The conversion of a ketone into an ω-chain-containing Corey lactone having two fluorine atoms at the 15-position by fluorination can be achieved by various known fluorination processes, for example, by using various nucleophilic fluorinating agents in inert solvents.

When a ketone as the starting material has a functional group liable to fluorinate during the fluorination, it is preferred to preliminarily protect the functional group by a protecting group. For example, when R^3 is a hydrogen atom, R^3 is preferably protected by a protecting group during the fluorination of the carbonyl group at the 15-position and then the protection group is removed.

The protecting groups include, for example, a triorganosilyl group, an acyl group, an alkyl group, an aralkyl group and a cyclic ether group. An acyl group to protect a hydroxyl group at the 11-position of a ketone used as the starting material may be the same as or different from the acyl group as R^3 of a fluorine-containing prostaglandin derivative (1). A fluorine-containing prostaglandin derivative (1) having an acyl group which is different from the acyl group used as the protecting group can be obtained by removing the protecting group and then introducing a different acyl group.

The triorganosilyl group is a group having three organic groups such as alkyl groups, aryl groups, aralkyl groups or alkoxy groups bonded to a silicon atom. Particularly preferred is a triorganosilyl group having three groups of at least one kind selected from the group consisting of lower alkyl groups and aryl groups. Specifically, a t-butyldimethylsilyl group, a t-butyldiphenylsilyl group, a triethylsilyl group, a triphenylsilyl group or a triisopropylsilyl group may, for example, be preferred.

As the acyl group, an acetyl group, a trifluoroacetyl group, a pivaloyl group, a benzoyl group or a p-phenylbenzoyl group is preferred, and as the cyclic ether group, a tetrahydropyranyl group or a tetrahydrofuranyl group is preferred. As the alkyl group or the aralkyl group which may have a substituent, an alkoxyalkyl group such as a methoxymethyl group, a 1-ethoxyethyl group or a 2-methoxyethoxymethyl group as well as a benzyl group, a methoxybenzyl group or a trityl group may, for example, be mentioned.

The protecting group for a hydroxyl group as mentioned above, can be converted to a hydroxyl group by a conventional method. For example, it can readily be converted to a hydroxyl group by methods disclosed in publications e.g. "Shinjikken Kagaku Koza 14 Syntheses and Reactions of Organic Compounds (I), (II) and (V)", published by Maruzen, and "Protective Groups in Organic Synthesis" written by T. W. Greene, published by J. Wiley & Sons.

The process for fluorination of a ketone having a carbonyl group at the 15-position as the starting material to an ω-chain-containing Corey lactone having two fluorine atoms at the 15-position uses a fluorinating agent. The fluorination is preferably carried out in an inert solvent and may be conducted in the presence of a base. The reaction temperature for the fluorination is usually from −150 to +100° C., preferably from −80 to +60° C. A fluorinating agent is used usually in an amount of from 0.5 to 20 parts by weight, preferably from 1 to 5 parts by weight, per part by weight of the substrate, a ketone as the starting material. The fluorinating agent used in the process for fluorinating a ketone having a carbonyl group at the 15-position as the starting material to an ω-chain-containing Corey lactone having two fluorine atoms at the 15-position is not particularly limited, and known or common nucleophilic fluorinating agents may be employed. For example, nucleophilic fluorinating agents disclosed in publications such as "Fluorine Chemistry" written by Tomoya Kitazume, Takashi Ishihara and Takeo Taguchi and published by Kodansha Scientific, may be used.

Specifically, dialkylaminosulfur trifluoride derivatives, tetrafluorophenylphophorane, fluoroalkylamine agents such as diethylamine-chlorotrifluoroethene adducts and diethylamine-hexafluoropropene adducts, hydrogen fluoride-amine complexes such as HF-pyridine and HF-triethylamine, silicon tetrafluoride, sulfur tetrafluoride, metal fluorides such as potassium fluoride, cesium fluoride and silver fluoride, and ammonium salts and phosphonium salts such as tetrabutylammonium fluoride, tetraethylammonium fluoride and tetrabutylphosphonium fluoride may, for example, be mentioned.

A carbonyl group can directly be fluorinated by using these nucleophilic fluorinating agents. A carbonyl group may be fluorinated after conversion of a ketone into its derivative such as an oxime, a hydrazone, a thioacetal or a diazo compound in order to improve its reactivity or inhibit side reactions. For example, the process of Olah et al. (Synlett 1990, 594, Synlett 1994, 425), the process of Katzenellenbogen et al. (J. Org. Chem. 51, 3508 (1986)), the process of Hiyama et al. (Synlett 1991, 909) and the process of Fujisawa et al. (J. Fluorine Chem. 71, 9 (1995)) are applicable.

Fluorination of a carbonyl group by a nucleophilic fluorinating agent is preferred in view of yield and selectivity. Dialkylaminosulfur trifluoride derivatives are particularly preferred as the nucleophilic fluorinating agent for fluorination, and specifically, morpholinosulfur trifluoride, piperidinosulfur trifluoride, diethylaminosulfur trifluoride, dimethylaminosulfur trifluoride and the like are preferred. As the inert solvent, a halogen-containing solvent, an etherial solvent, a hydrocarbon solvent, an ester solvent, a polar solvent, a mixture thereof is preferred. An inert solvent is used usually in an amount of from 2 to 500 parts by weight, preferably from 5 to 100 parts by weight, per part by weight of a ketone.

Preferable halogen-containing solvents are methylene chloride, chloroform, 1,2-dichloroethane, carbon tetrachloride, chlorobenzene and dichloropentafluoropropanes.

Preferable etherial solvents are diethyl ether, tetrahydrofuran [THF], 1,4-dioxane, dimethoxyethane, diglyme and t-butyl methyl ether.

Preferable hydrocarbon solvents are hexane, toluene, benzene, pentane, xylene and petroleum ether.

Preferable ester solvents are ethyl acetate and butyl acetate.

Preferable polar solvents are dimethyl sulfoxide, hexamethylphosphoramide [HMPA], 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone [DMPU], 1,3-dimethyl-2-imidazolidinone [DMI] and N,N,N',N'-tetramethylethylenediamine [TMEDA] (in the square brackets are abbreviations).

Particularly preferred solvents are methylene chloride, chloroform, 1,2-dichloroethane and toluene.

As the base used for the fluorination, amines such as tertiary amines and aromatic amines and salts of alkali

metals and alkaline earth metals are preferred. Specifically, triethylamine, diisopropylethylamine, pyridine, 2,6-lutidine, dimethylaminopyridine, sodium carbonate, potassium carbonate, sodium hydrogencarbonate and potassium hydrogencarbonate may be mentioned.

The lactone obtained by the above-mentioned fluorination is reduced to a lactol. For the reduction, a reducing agent is usually used in an inert solvent. For example, methods disclosed in publications such as "Shinjikken Kagaku Koza 15 Oxidation and reduction (II)" published by Maruzen and "Jikken Kagaku Koza 26 Organic Syntheses VIII, asymmetric synthesis, reduction, sugar and labeled compounds, fourth edition" published by Maruzen may be used. In the reduction, a reducing agent is used usually in amount of from 0.01 to 50 equivalents, preferably from 1 to 20 equivalents, per equivalent of a lactone. The reaction temperature is preferably from −150° to +100° C., particularly preferably from −80° to 0° C.

As reducing agents, diisobutylaluminum hydride [DIBAH], dialkylaluminum alkoxides, lithium aluminum hydride, tributyltin hydride, triphenyltin hydride, triethylsilane, trichlorosilane, dimethylphenylsilane, diphenylsilane, sodium borohydride, sodium trimethoxyborohydride, lithium tri(s-butyl)borohydride, potassium tri(s-butyl)borohydride, lithium triethylborohydride, lithium trisiamylborohydride, potassium trisiamylborohydride, zinc borohydride, calcium borohydride, lithium trialkoxyaluminum hydrides, sodium bis(2-methoxyethoxy)aluminum hydride, diborane, disiamylborane, thexylborane and 9-borabiscyclo[3.3.1]nonane may be mentioned. Diisobutylaluminum hydride [DIBAH], sodium bis(2-methoxyethoxy)aluminum hydride, disiamylborane and lithium tri(s-butyl)borohydride are preferred.

As the inert solvent used for the reduction, an etherial solvent, a hydrocarbon solvent, a polar solvent or a mixture thereof is preferred. Specific examples of the etherial solvent, the hydrocarbon solvent and the polar solvent are the etherial solvents, hydrocarbon solvents and polar solvents specifically described above for the fluorination. Above all, diethyl ether, THF, t-butyl methyl ether and toluene are particularly preferred. The configuration of the lactol produced by the reduction is not particularly limited.

As described above, a phosphorane is produced from the corresponding phosphonium salt in an inert solvent in the presence of a base. The resulting phosphorane is not usually isolated and directly used for the Wittig reaction with a lactol. For production of a phosphorane from the corresponding phosphonium salt, methods disclosed in publications such as "Shinjikken Kagaku Koza 14 Syntheses and reactions of organic compounds (I)" published by Maruzen, and "Jikken Kagaku Koza 19 Organic Synthesis I, hydrocarbons and halogen compounds, fourth edition" published by Maruzen and the method of Schaaf et al. (J. Med. Chem. 22, 1340 (1979)) may, for example, be employed.

Z in the phosphorane or the phosphonium salt is usually a hydroxyl group (namely, OR^4 wherein R^4 is a hydrogen atom) although it may be any of those described above for Z. In such a case, the reaction of the phosphorane with lactol gives a fluorine-containing prostaglandin derivative wherein Z is a hydroxyl group. In order to obtain a fluorine-containing prostaglandin derivative wherein Z is not a hydroxyl group, it is preferred to convert Z of a fluorine-containing prostaglandin derivative from a hydroxyl group to a different group. A fluorine-containing prostaglandin derivative wherein Z is not a hydroxyl group can be prepared from a phosphorane or its precursor having a group other than a hydroxyl group as Z.

Conversion of a phosphonium salt wherein Z is $—NHCOR^5$ or $—NHSO_2R^6$ to a phosphorane is sometimes accompanied by replacement of the hydrogen atom bonded to the nitrogen atom in $—NHCOR^5$ or $—NHSO_2R^6$ by a metal ion. Consequently, in such a case, the product of the Wittig reaction of the resulting phosphorane with a lactol also has a metal ion at the corresponding site. The metal ion is attributed to the metal ion (specifically, an alkali metal ion or an alkaline earth metal ion) in the base used for conversion of a phosphonium salt into a phosphorane. The metal ion can eventually be replaced by a hydrogen atom through hydrolysis or other processes.

Examples of the phosphonium salts include, for example, the following compounds. These phosphonium salts yield the corresponding phosphoranes.

(4-Carboxybutyl)triphenylphosphonium bromide;

(4-carboxy-3-oxabutyl)triphenylphosphonium bromide;

[4-(N-methanesulfonyl)carbamoylbutyl]triphenylphosphonium bromide;

[4-(N-benzoyl)carbamoylbutyl]triphenylphosphonium bromide;

(4-carboxybutyl)tri(o-tolyl)phosphonium bromide;

(4-carboxybutyl)tri(m-tolyl)phosphonium bromide; and

(4-carboxybutyl)tri(p-tolyl)phosphonium bromide.

A phosphorane is used usually in an amount of from 0.1 to 20 equivalents, preferably from 1 to 10 equivalents, per equivalent of a lactol. The reaction of a lactol with a phosphorane is classified as the so-called Wittig reaction. Ordinary conditions for the Wittig reaction are applicable to the reaction of a lactol with a phosphorane according to the present invention. In particular, it is preferred to carry out the reaction under basic conditions in an inert solvent. The reaction temperature is usually from −150 to +200° C., preferably from −80° to +100° C.

A base is used usually in an amount of from 1 to 20 equivalents, preferably from 2 to 10 equivalents, per equivalent of a lactol. A base of the proper kind should be used in view of the acidity of the hydrogen atom bonded to the carbon atom at the α-position based on the phosphorus atom of a phosphonium salt as the precursor of a phosphorane and the stability of the resulting phosphorane. Such a base can be selected, for example, from the following bases.

Sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium methoxide, sodium ethoxide, triethylamine, diisopropylethylamine, pyridine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,8-diazabicyclo[5.4.0]undec-7-ene, potassium t-butoxide, lithium amide, sodium amide, potassium amide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, lithium isopropylcyclohexylamide, lithium 2,2,6,6-tetramethylpiperidine, lithium bis(trimethylsilyl)amide, sodium diethylamide, sodium bis(trimethylsilyl)amide, potassium 3-aminopropylamide, potassium bis(trimethylsilyl)amide, lithium hydride, sodium hydride, potassium hydride, sodium methylsulfinylmethylide, n-butyllithium, s-butyllithium, t-butyllithium, methyllithium, phenyllithium, lithium naphthalenide, lithium biphenylide and tritylsodium.

Among these bases, potassium carbonate, potassium t-butoxide, lithium amide, sodium amide, potassium amide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, lithium isopropylcyclohexylamide, lithium 2,2,6,6-tetramethylpiperidine, lithium bis(trimethylsilyl)amide, sodium diethylamide, sodium bis(trimethylsilyl)amide, potassium 3-aminopropylamide, potassium bis(trimethylsilyl)amide and sodium methylsulfi-

nylmethylide are preferred. Potassium t-butoxide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl) amide and sodium methylsulfinylmethylide are particularly preferred.

As the inert solvent, an etherial solvent, a hydrocarbon solvent, a polar solvent, an aqueous solvent, an alcoholic solvent or a solvent mixture thereof is preferred. An inert solvent is used usually in an amount of from 5 to 1000 parts by weight, preferably from 10 to 100 parts by weight, per part by weight of a lactol. As specific examples of the etherial solvent, the hydrocarbon solvent and the polar solvent, the etherial solvents, the hydrocarbon solvents and the polar solvents specifically described above for the fluorination are preferred. As the aqueous solvent, water or a solvent mixture of water with an alcoholic solvent is preferred. As the alcoholic solvent, methanol, ethanol, t-butanol and t-amyl alcohol are preferred. Particularly preferred solvents are diethyl ether, THF, 1,2-dimethoxyethane, t-butyl methyl ether and toluene.

Z of the resulting fluorine-containing prostaglandin derivative can be converted into a different kind of Z, if necessary. For example, a fluorine-containing prostaglandin derivative wherein Z is a hydroxyl group can optionally be converted into an ester, a salt of a carboxylic acid, an acyl amide, sulfonamide or a thioester by a conventional method.

For esterification of Z, ordinary methods such as methods disclosed in publications such as "Shinjikken Kagaku Koza 14 Syntheses and reactions of organic compounds (II)" published by Maruzen may be used. Esterification by condensation with an alcohol or a phenol, esterification with an O-alkylating agent, esterification by use of an alkene or an alkyne, esterification with a dialkyl sulfate or a halogenated hydrocarbon may be mentioned.

For conversion into an acyl amide or a sulfonamide, the method of Tithereley et al. (J. Chem. Soc. 85, 1673 (1904)), the method of Lynch et al. (Can. J. Chem. 50, 2143 (1972)), the method of Davidson et al. (J. Am. Chem. Soc. 80, 376 (1958)) and the like can be used. Alternatively, conversion of a carboxylic acid into an acid halide or a reactive ester followed by condensation with an amide or a sulfonamide or reaction of a carboxylic acid with an amine to produce an amide followed by acylation or sulfonylation may be employed.

For conversion of Z into a thioester, methods described in publications such as "Shinjikken Kagaku Koza 14 Syntheses and reactions of organic compounds (III)" published by Maruzen and "protective Groups in Organic Syntheses" written by T. W. Greene and published by J. Wiley & Sons may be employed. For example, a process comprising conversion of a carboxylic acid is converted into an acid halide or a reactive ester and then reacted with a thiol may be employed.

Specific examples of the compound of the formula (I) are given below, and, however, the compound is not limited to these specific examples.

15-Deoxy-15,15-difluoroprostaglandin $F_{2\alpha}$,

15-deoxy-15,15-difluoroprostaglandin $F_{2\alpha}$ methyl ester,

15-deoxy-15,15-difluoroprostaglandin $F_{2\alpha}$ ethyl ester,

15-deoxy-15,15-difluoroprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3-trifluoromethylphenoxy)-15-deoxy-15;15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

17-phenyl-15-deoxy-15,15-difluoro-18,19,20-trinorprostaglandin $F_{2\alpha}$ methyl ester,

17-phenyl-15-deoxy-15,15-difluoro-18,19,20-trinorprostaglandin $F_{2\alpha}$ ethyl ester,

17-phenyl-15-deoxy-15,15-difluoro- 18,19,20-trinorprostaglandin $F_{2\alpha}$ isopropyl ester,

15-deoxy-15,15-difluoro-13,14-dihydroprostaglandin $F_{2\alpha}$ methyl ester,

15-deoxy-15,15-difluoro-13,14-dihydroprostaglandin $F_{2\alpha}$ ethyl ester,

15-deoxy-15,15-difluoro-13,14-dihydroprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester;

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester;

16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

17-phenyl-15-deoxy-15,15-difluoro-13,14-dihydro-18,19,20-trinorprostaglandin $F_{2\alpha}$ methyl ester,

17-phenyl-15-deoxy-15,15-difluoro-13,14-dihydro-18,19,20-trinorprostaglandin $F_{2\alpha}$ ethyl ester,

17-phenyl-15-deoxy-15,15-difluoro-13,14-dihydro-18,19,20-trinorprostaglandin $F_{2\alpha}$ isopropyl ester;

15-deoxy-15,15-difluoro-3-oxaprostaglandin $F_{2\alpha}$,

15-deoxy-15,15-difluoro-3-oxaprostaglandin $F_{2\alpha}$ methyl ester,

15-deoxy-15,15-difluoro-3-oxaprostaglandin $F_{2\alpha}$ ethyl ester,

15-deoxy-15,15-difluoro-3-oxaprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester;

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

16-phenoxy-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-phenoxy-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-phenoxy-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester;

17-phenyl-15-deoxy-15,15-difluoro-3-oxa-18,19,20-trinorprostaglandin $F_{2\alpha}$ methyl ester,

17-phenyl-15-deoxy-15,15-difluoro-3-oxa-18,19,20-trinorprostaglandin $F_{2\alpha}$ ethyl ester,

17-phenyl-15-deoxy-15,15-difluoro-3-oxa-18,19,20-trinorprostaglandin $F_{2\alpha}$ isopropyl ester,

15-deoxy-15,15-difluoro-9-pivaloylprostaglandin $F_{2\alpha}$ methyl ester,

15-deoxy-15,15-difluoro-9-pivaloylprostaglandin $F_{2\alpha}$ ethyl ester,

15-deoxy-15,15-difluoro-9-pivaloylprostaglandin $F_{2\alpha}$ isopropyl ester;

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester;

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester;

16-phenoxy-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-phenoxy-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-phenoxy-15-deoxy-15,15-difluoro-9-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

17-phenyl-15-deoxy-15,15-difluoro-9-pivaloyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ methyl ester,

17-phenyl-15-deoxy-15,15-difluoro-9-pivaloyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ ethyl ester,

17-phenyl-15-deoxy-15,15-difluoro-9-pivaloyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ isopropyl ester;

15-deoxy-15,15-difluoro-11-pivaloylprostaglandin $F_{2\alpha}$ methyl ester,

15-deoxy-15,15-difluoro-11-pivaloylprostaglandin $F_{2\alpha}$ ethyl ester,

15-deoxy-15,15-difluoro-11-pivaloylprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester;

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester;

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester,

16-phenoxy-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester,

16-phenoxy-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester,

16-phenoxy-15-deoxy-15,15-difluoro-11-pivaloyl-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester;

17-phenyl-15-deoxy-15,15-difluoro-11-pivaloyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ methyl ester,

17-phenyl-15-deoxy-15,15-difluoro-11-pivaloyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ ethyl ester,

17-phenyl-15-deoxy-15,15-difluoro-11-pivaloyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ isopropyl ester,

15-deoxy-15,15-difluoroprostaglandin $F_{2\alpha}$ 1,9-lactone,

15-deoxy-15,15-difluoroprostaglandin $F_{2\alpha}$ 1,11-lactone,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 1,9-lactone;

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 1,11-lactone,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 1,9-lactone,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 1,11-lactone,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 1,9-lactone,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 1,11-lactone,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 1,9-lactone;

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 1,11-lactone,

16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 1,9-lactone,

16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ 1,11-lactone,

17-phenyl-15-deoxy-15,15-difluoro-18,19,20-trinorprostaglandin $F_{2\alpha}$ 1,9-lactone,

17-phenyl-15-deoxy-15,15-difluoro-18,19,20-trinorprostaglandin $F_{2\alpha}$ 1,11-lactone;

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$;

16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$,

17-phenyl-15-deoxy-15,15-difluoro-18,19,20-trinorprostaglandin $F_{2\alpha}$,

15-deoxy-15,15-difluoro-13,14-dihydroprostaglandin $F_{2\alpha}$,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$,

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$;

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$,

16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$,

17-phenyl-15-deoxy-15,15-difluoro-13,14-dihydro-18,19,20-trinorprostaglandin $F_{2\alpha}$,

15-deoxy-15,15-difluoro-3-oxa-prostaglandin $F_{2\alpha}$,

16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$;

16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$,

16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$,

16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$,

16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-3-oxa-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$,

17-phenyl-15-deoxy-15,15-difluoro-13,14-dihydro-3-oxa-18,19,20-trinorprostaglandin $F_{2\alpha}$;

N-methanesulfonyl-15-deoxy-15,15-difluoroprostaglandin $F_{2\alpha}$ carboxamide,

N-methanesulfonyl-16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ carboxamide,

N-methanesulfonyl-16-(3,4-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ carboxamide,

N-methanesulfonyl-16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ carboxamide,

N-methanesulfonyl-16-(3-trifluoromethylphenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ carboxamide,

N-methanesulfonyl-16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ carboxamide, and

N-methanesulfonyl-17-phenyl-15-deoxy-15,15-difluoro-18,19,20-trinorprostaglandin $F_{2\alpha}$ carboxamide.

The fluorine-containing prostaglandin derivative of the formula (I) has asymmetric carbon atoms in its structure and thus has various stereoisomers and optical isomers. The fluorine-containing prostaglandin derivatives of the present invention include all of such stereoisomers, optical isomers and their mixtures.

The compounds of the present invention (the fluorine-containing prostaglandin derivatives and their salts) are superior to known naturally occurring $PGF_{2\alpha}$ in the effect of lowering intraocular pressure. They hardly irritate the eye and have very little effect on the ocular tissues such as the cornea, the iris and the conjunctiva. Further, they are unlikely to decompose through metabolic processes such as hydrolysis and oxidation and stable in the body. They also easily penetrate the cornea and are easily absorbed by the eye. For these reasons, they are very useful as medicines. In addition, they solve the problem of the stimulation of melanogenesis by conventional $PGF_{2\alpha}$ derivatives and are compounds which hardly stimulate melanogenesis. Therefore, the medicine of the present invention is effective as a therapeutic agent, particularly for glaucoma or ocular hypertension.

The medicine of the present invention is a pharmaceutical containing the compound of the present invention as an active ingredient and typically applied to the eye, for example, in drops. As its dosage forms, external preparations such as eye drops and ophthalmic ointments and injections are mentioned, and the compounds of the present invention are formulated by using common techniques. For example, in the case of eye drops, isotonicities such as sodium chloride and concentrated glycerine, buffering agents such as sodium phosphate and sodium acetate, surfactants such as polyoxyethylene sorbitane monoolate (hereinafter referred to as polysorbate 80), polyoxyl 40 stearate and polyoxyethylene hydrogenated castor oil, stabilizers such as sodium citrate and sodium edetate and antiseptics such as benzalkonium chloride and paraben are optionally used to prepare the medicine of the present invention. The pH should be within a range acceptable for ocular medicines and is preferably from 4 to 8.

Although the dose depends on the condition and the age of the patient and the dosage form, in the case of an ophthalmic solution, it is applied to the eye at a concentration of 0.0001 to 1% (w/v), preferably from 0.0005 to 0.5% (w/v) once or a couple of times a day.

Now, the present invention will be described in further detail with reference to Examples. However, the present invention is by no means restricted to such specific Examples. In Examples 1 to 21, compounds of the present invention were prepared. Example 22 illustrates formulations of the medicines of the present invention, and in Example 23, a pharmacological tests of medicines of the present invention are presented.

EXAMPLE 1

Preparation of (1S,5R,6R,7R)-2-oxa-7-benzoyloxy-6-[(1E)-4-(3-chlorophenoxy)-3-oxo-1-butenyl] bicyclo[3.3.0]octan-3-one

To a solution of 26.5 g of dimethyl 2-oxo-3-(3-chlorophenoxy)propylphosphonate in THF (260 ml), 3.39 g of lithium chloride and 10.9 ml of triethylamine were added under cooling with ice. After 15 minutes of stirring, a solution of 18.1 g of (1S,5R,6R,7R)-6-formyl-7-benzoyloxy-2-oxabicyclo[3.3.0]octan-3-one in methylene chloride (65 ml) was added. After 1 hour of stirring at 0° C., the reaction solution was poured into a 1/1 mixture of saturated aqueous ammonium chloride/ethyl acetate, and the resulting mixture was allowed to separeate. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was dried and concentrated. The concentrate was purified by silica gel column chromatography (hexane/ethyl acetate 1/3–2/1) to obtain 19.8 g of the above-identified compound.

^{1}H NMR($CDCl_3$); δ 2.2–2.9(m,6H),4.67(s,2H),5.09(m, 1H), 5.34(m,1H),6.56(d,J=15.9 Hz,1H),6.73–6.97(m,4H), 7.18 (m,1H),7.44(m,2H),7.58(m,1H),7.97(m,2H).

EXAMPLE 2

Preparation of (1S,5R,6R,7R)-2-oxa-7-benzoyloxy-6-[(1E)-3,3-difluoro-4-(3-chlorophenoxy)- 1-butenyl]bicyclo[3.3.0]octan-3-one

To a solution of 5.00 g of the enone prepared in Example 1 in methylene chloride (150 ml), 19.8 g of morpholinosulfur trifluoride was added at 0° C. The resulting mixture was stirred at room temperature for 180 hours, then poured into saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The extract was purified by silica gel column chromatography (hexane/ethyl acetate 2/1) to obtain 3.47 g of the above-identified compound.

^{1}H NMR($CDCl_3$): δ 2.2–3.0(m,6H),4.13(m,2H),5.09(m, 1H), 5.30(m,1H),5.87(dt,J=15.6,11.2 Hz,1H),6.15(m,1H), 6.72 (m,1H),6.84(m,1H),6.97(m,1H),7.18(m,1H),7.41(m, 2H),7.55 (m,1H),7.96(m,2H). ^{19}F NMR($CDCl_3$): −104.1 (m).

EXAMPLE 3

Preparation of (1S,5R,6R,7R)-2-oxa-7-hydroxy-6-[(1E)-3,3-difluoro-4-(3-chlorophenoxy)-1-butenyl] bicyclo[3.3.0]octan-3-one

3.47 g of the fluoride prepared in Example 2 was dissolved in 40 ml of methanol, and 645 mg of potassium carbonate was added. The mixture was stirred at room temperature for 3 hours. After the pH was adjusted to about 7 with acetic acid, water was added, and the mixture was extracted with ethyl acetate. The extract was purified by silica gel column chromatography (hexane/ethyl acetate 1/2–2/3) to obtain 2.69 g of the above-identified compound.

^{1}H NMR($CDCl_3$): δ 2.0–2.8(m,6H),4.09–4.21(m,3H), 4.95(m,1H),5.84(dt,J=15.6,11.2 Hz,1H),6.07(m,1H),6.81 (m,1H),6.91(m,1H),7.01(m,1H),7.23(m,1H). ^{19}F NMR ($CDCl_3$): −103.7(m).

EXAMPLE 4

Preparation of (1S,5R,6R,7R)-2-oxa-3,7-dihydroxy-6-[(1E)-3,3-difluoro-4-(3-chlorophenoxy)-1-butenyl] bicyclo[3.3.0]octane

To a solution of 1.57 g of (1S,5R,6R,7R)-2-oxa-7-hydroxy-6-[(1E)-3,3-difluoro-4-(3-chlorophenoxy)-1-butenyl]bicyclo[3.3.0]octan-3-one prepared in Example 3 in THF (50 ml), a toluene solution (1M, 17.5 ml) of diisobutylaluminum hydride was added at −78° C., and the mixture was stirred for 30 minutes. Water (20 ml) and 1N hydrochloric acid (40 ml) were added, and the mixture was

extracted with ethyl acetate. The extract was purified by silica gel column chromatography (hexane/ethyl acetate 1/1–3/2) to obtain 1.26 g of the above-identified compound.

^{1}H NMR($CDCl_3$): δ 2.0–2.6(m,6H),2.89–3.10(m,1H), 3.98(m,1H),4.18(m,2H),4.66(m,1H),5.57–5.67(m,1H),5.79 (m,1H),6.11(m,1H),6.81(m,1H),6.92(m,1H),6.99(m,1H), 7.22(m,1H). ^{19}F NMR($CDCl_3$): −103.4(m).

EXAMPLE 5

Preparation of 16-(3-chlorophenoxy)-15-deoxy- 15, 15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester

To a solution of 6.21 g of 4-carboxybutyltriphenylphosphonium bromide in THF (80 ml), a toluene solution (0.5M, 56 ml) of potassium bis (trimethylsilyl)amide was added, and the mixture was stirred at room temperature for 30 minutes. A solution of 1.26 g of the lactol prepared in Example 4 in THF (30 ml) was added at −20° C., and the mixture was stirred at room temperature for 1 hour. Water was added to terminate the reaction, and the reaction mixture was washed with diethyl ether. The aqueous layer was acidified and then extracted with ethyl acetate. The extract was dried, and then the solvent was evaporated off to obtain 1.56 g of a crude carboxylic acid.

To a solution of 1.56 g of the carboxylic acid thus obtained in acetone (14 ml), 4.28 g of 1,8-diazabicyclo [5.4.0]undec-7-ene and 5.38 g of 2-iodopropane were added, and the mixture was stirred for 17 hours. The reaction mixture was diluted with ethyl acetate, then washed with saturated aqueous sodium chloride, 3% aqueous citric acid and aqueous sodium bicarbonate, dried and concentrated. The concentrate was purified by silica gel column chromatography (hexane/ethyl acetate 1/1) to obtain 0.91 g of the above-identified compound.

^{1}H NMR($CDCl_3$): δ 1.22(d,J=6.4 Hz,6H),1.6–2.8(m, 14H), 4.03(m,1H),4.18(t,J=11.7 Hz,2H),4.21(m,1H),4.99 (m,1H), 5.38(m,1H),5.78(dt,J=15.6,11.2 Hz,1H),6.10(m, 1H),6.81 (m,1H),6.92(m,1H),6.98(m,1H),7.21(m,1H). ^{19}F NMR($CDCl_3$): −103.3(m).

EXAMPLE 6

Preparation of 16-(3-chlorophenoxy)-15-deoxy-15, 15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$

To a solution of 440 mg of 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester prepared in Example 5 in ethanol (13 ml), 0.2N aqueous sodium hydroxide (11.3 ml) was added, and the mixture was stirred at room temperature for 22 hours. The reaction solution was poured into saturated aqueous sodium bicarbonate and washed with toluene. The reaction solution was adjusted to pH 1 with 2N hydrochloric acid and then extracted with ethyl acetate. The extract was dried and concentrated to obtain 423 mg of the above-identified compound.

^{1}H NMR($CDCl_3$): δ 1.6–2.5(m,14H),4.04(m,1H), 4.14–4.20(m,3H),5.38(m,2H),5.78(dt,J=15.6,11.2 Hz,1H), 6.09 (m,1H),6.81(m,1H),6.92(m,1H),6.98(m,1H),7.21(m, 1H). ^{19}F NMR($CDCl_3$): −103.4(m).

EXAMPLE 7

Preparation of 16-(3-chlorophenoxy)-15-deoxy-15, 15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester

To a solution of 200 mg of 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ prepared in Example 6 in acetone (2 ml), 275 mg of 1,8-diazabicyclo[5.4.0]undec-7-ene and 316 mg of iodoethane were added, and the resulting reaction solution was stirred for 5 hours. The reaction solution was diluted with ethyl acetate, then washed with saturated aqueous sodium chloride, 3% aqueous citric acid and aqueous sodium bicarbonate, dried and concentrated. The concentrate was purified by silica gel column chromatography (hexane/ethyl acetate 1/1) to obtain 82 mg of the above-identified compound.

^{1}H NMR($CDCl_3$); δ 1.25(t,J=7.3 Hz,3H),1.6–2.6(m, 14H), 4.04(m,1H),4.12(q,J=7.3 Hz,2H),4.15–4.21(m,3H), 5.39(m,2H), 5.78(dt,J=15.6,11.2 Hz,1H),6.11(m,1H),6.81 (m,1H),6.92 (m,1H),6.99(m,1H),7.22(m,1H). ^{19}F NMR ($CDCl_3$): −103.4(m).

EXAMPLE 8

Preparation of 16-(3-chlorophenoxy)-15-deoxy-15, 15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester

To a solution of 221 mg of 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ in a solvent mixture of methanol (1 ml) and benzene (4 ml), trimethylsilyldiazomethane (10% hexane solution, 2.5 ml) was added, and the resulting reaction solution was stirred for 30 minutes. Acetic acid was added dropwise to terminate the reaction, and the reaction solution was concentrated. The concentrate was purified by silica gel column chromatography (hexane/ethyl acetate 1/1) to obtain 65 mg of the above-identified compound.

^{1}H NMR($CDCl_3$): δ 1.6–2.5(m,14H),3.66(s,3H),4.04(m, 1H), 4.15–4.21(m,3H),5.39(m,2H),5.78(dt,J=15.6,11.2 Hz,1H), 6.11(m,1H),6.81(m,11H),6.92(m,1H),6.99(m,1H), 7.22(m,1H). ^{19}F NMR($CDCl_3$): −103.4(m).

EXAMPLE 9

Preparation of 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester

The above-identified compound was prepared in the same manners as in Examples 1 to 5 using (1S,5R,6R,7R)-6-formyl-7-benzoyloxy-2-oxabicyclo[3.3.0]octan-3-one and dimethyl 2-oxo-3-phenoxypropylphosphonate.

^{1}H NMR($CDCl_3$): δ 1.22(d,J=6.4 Hz,6H),1.59(m,1H), 1.66 (m,2H),1.83(m,1H),2.0–2.4(m,7H),2.47(m,1H),4.02 (m,1H), 4.19(t,J=11.5 Hz,2H),4.19(m,1H),4.99(m,1H),5.38 (m,2H),5.80 (dt,J=15.6,11.2 Hz,1H),6.10(m,1H),6.91(m, 2H),7.00(m,1H), 7.30(m,2H). ^{19}F NMR($CDCl_3$): −103.7 (m).

The following compounds were prepared in the respective steps in the present Example.

(1S,5R,6R,7R)-2-oxa-7-benzoyloxy-6-[(1E)-4-phenoxy-3-oxo-1-butenyl]bicyclo[3.3.0]octan-3-one

^{1}H NMR($CDCl_3$): δ 2.29(ddd,J=15.6,4.9,0.2 Hz,1H), 2.45–2.51(m,1H),2.60(dt,J=15.6,6.6 Hz,1H),2.83–2.95(m, 3H), 4.67(s,2H),5.08(td,J=4.6,1.7 Hz,1H),5.31(m,1H),6.60 (dd, J=15.6,1.0 Hz,1H),6.84–6.87(m,2H),6.91(dd,J=15.6, 7.8 Hz,1H),6.98(t,J=7.3 Hz,1H),7.25–7.29(m,2H),744 (t,J= 7.3 Hz,2H),7.58(dt,J=7.3,1.2 Hz,1H),7.97(dd,J=8.3, 1.2 Hz,2H).

(1S,5R,6R,7R)-2-oxa-7-benzoyloxy-6-[(1E)-3,3-difluoro-4-phenoxy-1-butenyl]bicyclo[3.3.0]octan-3-one

^{1}H NMR($CDCl_3$): δ 2.2–2.9(m,6H),4.17(t,J=11.5 Hz,2H), 5.09(m,1H),5.29(m,1H),5.89(dt,J=15.6,11.0 Hz,1H),6.15

(m,1H),6.85(d,J=7.8 Hz,2H),6.99(t,J=7.3 Hz,1H),7.27(m, 2H), 7.41(m,2H),7.55(t,J=7.3 Hz,1H),7.97(d,J=7.3 Hz,2H). ^{19}F NMR($CDCl_3$): −104.0(m).

(1S,5R,6R,7R)-2-oxa-7-hydroxy-6-[(1E)-3,3-difluoro-4-phenoxy-1-butenyl]bicyclo[3.3.0]octan-3-one

^{1}H NMR($CDCl_3$): δ 2.0–2.8(m,6H),4.09(m,1H),4.20(t, J=11.5 Hz,2H),4.94(m,1H),5.84(dt,J=15.6,11.2 Hz,1H),6.07 (m,1H),6.91(d,J=7.8 Hz,2H),7.02(t,J=7.3 Hz,1H),7.31(m, 2H). ^{19}F NMR($CDCl_3$): −103.6(m).

(1S,5R,6R,7R)-2-oxa-3,7-dihydroxy-6-[(1E)-3,3-difluoro-4-phenoxy-1-butenyl]bicyclo[3.3.0]octane

^{1}H NMR($CDCl_3$): δ 1.8–2.9(m,6H),3.96(m,1H),4.19 (t,J= 11.5 Hz,2H),4.60–4.71(m,1H),5.56–5.65(m,1H),5.82 (m,1H),6.11(m,1H),6.91(d,J=8.3 Hz,2H),7.00(m,1H),7.30 (t,J=7.8 Hz,2H). ^{19}F NMR($CDCl_3$): −103(m).

EXAMPLE 10

Preparation of 16-phenoxy-15-deoxy-15,15-difluoro- 17,18,19,20-tetranorprostaglandin $F_{2\alpha}$

The above-identified compound was prepared in the same manner as in Example 6 using 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester prepared in Example 9.

^{1}H NMR($CDCl_3$): δ 1.60(m,1H),1.67(m,2H),1.83(m,1H), 2.0–2.5(m,8H),2.47(m,1H),4.03(m,1H),4.18(t,J=11.7 Hz,2H), 4.18(m,1H),5.36(m,2H),5.80(dt,J=15.8,10.5 Hz,1H),6.09 (m,1H),6.91(m,2H),6.99(m,1H),7.29(m,2H). ^{19}F NMR($CDCl_3$): −103.7(m).

EXAMPLE 11

Preparation of 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester

The above-identified compound was prepared in the same manner as in Example 7 using 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ prepared in Example 10.

^{1}H NMR($CDCl_3$): δ 1.25(t,J=7.2 Hz,3H),1.55–1.75(m, 3H), 1.85(m,1H),2.05–2.50(m,8H),4.01(m,1H),4.12(q,J= 7.2 Hz,2H), 4.20(t,J=11.7 Hz,2H),4.21(m,1H),5.38(m,2H), 5.81(dt,J=11.1, 15.7 Hz,1H),6.10(ddt,J=2.0,9.1,15.7 Hz,1H) ,6.91(m,2H),7.00 (m,1H),7.30(m,2H). ^{19}F NMR($CDCl_3$): −103.3(m).

EXAMPLE 12

Preparation of 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester

The above-identified compound was prepared in the same manner as in Example 8 using 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ prepared in Example 10.

^{1}H NMR($CDCl_3$): δ 1.60(m,1H),1.67(m,2H),1.84(m,1H), 2.0–2.4(m,8H),2.47(m,1H),3.66(s,3H),4.02(m,1H),4.20 (t,J=12.0 Hz,2H),4.20(m,1H),5.38(m,2H),5.80(dt,J=16.4, 10.8 Hz,1H),6.10(m,1H),6.91(m,2H),7.00(m,1H),7.30(m, 2H). ^{19}F NMR($CDCl_3$): −103.7(m).

EXAMPLE 13

Preparation of 16-(3,5-dichlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester

The above-identified compound was prepared in the same manners as in Examples 1 to 5 using (1S,5R,6R,7R)-6-formyl-7-benzoyloxy-2-oxabicyclo[3.3.0]octan-3-one and dimethyl 2-oxo-3-(3,5-dichlorophenoxy) propylphosphonate.

^{1}H NMR($CDCl_3$): δ 1.23(d,J=6.1 Hz,6H),1.6–2.5(m, 12H), 4.03(m,1H),4.17(t,J=11.4 Hz,2H),4.22(m,1H),5.00 (m,1H),5.39 (t,J=5.0 Hz,2H),5.76(m,1H),6.11(m,1H),6.83 (d,J=1.8 Hz,2H), 7.02(t,J=1.8 Hz,1H). ^{19}F NMR($CDCl_3$): −103.5(m).

The following compounds were prepared in the respective steps in the present Example.

(1S,5R,6R,7R)-2-oxa-7-benzoyloxy-6-[(1E)-4-(3,5-dichlorophenoxy)-3-oxo-1-butenyl]bicyclo[3.3.0]octan-3-one

^{1}H NMR($CDCl_3$): δ 2.31(ddd,J=15.6,4.9,2.0 Hz,1H),2.51 (m,1H),2.65(dt,J=15.6,6.5 Hz,1H),2.87–2.98(m,3H),4.67 (s,2H),5.11(dt,J=6.5,2.0 Hz,1H),5.35(m,1H),6.54(d, J=16.1 Hz,1H),6.77(d,J=2.0 Hz,2H),6.92(dd,J=16.1,7.8 Hz,1H), 6.99(t,J=2.0 Hz,1H),7.45(m,2H),7.60(m,1H),7.98(m,2H).

(1S,5R,6R,7R)-2-oxa-7-benzoyloxy-6-[(1E)-3,3-difluoro-4-(3,5-dichlorophenoxy)-1-butenyl]bicyclo[3.3.0] octan-3-one

^{1}H NMR($CDCl_3$): δ 2.2–2.9(m,6H),4.12(m,2H),5.08(m, 1H), 5.31(q,J=6.1 Hz,1H),5.85(m,1H),6.14(dd,J=15.9,7.6 Hz,1H), 6.76(d,J=1.7 Hz,2H),6.98(t,J=1.7 Hz,1H),7.4–7.6 (m,3H), 7.94(m,2H). ^{19}F NMR($CDCl_3$): −104(m).

(1S,5R,6R,7R)-2-oxa-7-hydroxy-6-[(1E)-3,3-difluoro-4-(3,5-dichlorophenoxy)-1-butenyl]bicyclo[3.3.0]octan-3-one

^{1}H NMR($CDCl_3$): δ 2.04(m,1H),2.4–2.9(m,5H),4.08(dt, J=6.1,6.4 Hz,1H),4.15(t,J=11.5 Hz,2H),4.95(dt,J=4.4,2.4 Hz, 1H),5.79(dt,J=15.9,11.2 Hz,1H),6.06(ddt,J=15.9,8.0,1.0 Hz, 1H),6.81(d,J=1.7 Hz,2H),7.00(t,J=1.7 Hz,1H). ^{19}F NMR($CDCl_3$): −103(m).

(1S,5R,6R,7R)-2-oxa-3,7-dihydroxy-6-[(1E)-3,3-difluoro-4-(3,5-dichlorophenoxy)-1-butenyl]bicyclo[3.3.0] octane

^{1}H NMR($CDCl_3$): δ 1.8–2.9(m,6H),3.97(m,1H),4.15(t, J=12.2 Hz,2H),4.65(m,1H),5.55–5.65(m,1H),5.77(m,1H), 6.07 (m,1H),6.82(m,2H),7.01(m,1H). ^{19}F NMR($CDCl_3$): −103.5(m).

EXAMPLE 14

Preparation of (1S,5R,6R,7R)-2-oxa-7-benzoyloxy-6-[4-(3-chlorophenoxy)-13-oxobutyl]bicyclo[3.3.0] octan-3-one

5% Pd-C (580 mg) was suspended in a solution of 4.08 g of the enone prepared in Example 1 in ethyl acetate (80 ml), and the suspension was stirred under a hydrogen atmosphere at room temperature for 2 hours. The reaction mixture was filtered through Celite and then concentrated. The concentrate was purified by silica gel column chromatography (hexane/ethyl acetate 1/1) to obtain 3.89 g of the above-identified compound.

^{1}H NMR($CDCl_3$): δ 1.68(m,1H),1.81(m,1H),2.13(m,1H), 2.35–2.52(m,3H),2.68(m,1H),2.78–2.95(m,3H),4.56(s,2H), 5.10(dt,J=1.0,6.0 Hz,1H),5.20(ddd,J=2.9,3.3,6.0 Hz,1H), 6.74 (m,1H),6.85(m,1H),6.97(m,1H),7.19(m,1H),7.43(m, 2H),7.55 (m,1H),7.97(m,2H).

EXAMPLE 15

Preparation of 16-(3-chlorophenoxy)-15-deoxy-15, 15-difluoro-13, 14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester

The above-identified compound was prepared in the same manners as in Examples 2 to 5 using the ketone prepared in Example 14.

^{1}H NMR($CDCl_3$): δ 1.22(d,J=6.4 Hz,6H),1.43(m,2H), 1.65–1.75(m,4H),1.9–2.5(m,10H),3.95(m,1H),4.10(m,2H), 4.20 (m,1H),5.00(m,1H),5.41(m,2H),6.82(m,1H),6.93(m, 1H),6.99 (m,1H),7.22(m,1H). ^{19}F NMR($CDCl_3$): −105.7 (m).

The following compounds were prepared in the respective steps in the present Example.

(1S,5R,6R,7R)-2-oxa-7-benzoyloxy-6-[3,3-difluoro-4-(3-chlorophenoxy)butyl]bicyclo[3.3.0]octan-3-one

^{1}H NMR($CDCl_3$): δ 1.68(m,2H),2.2–2.5(m,6H),2.72(m, 1H), 2.94(dd,J=18.3,10.7 Hz,1H),4.11(t,J=11.5 Hz,2H),5.12 (dt, J=5.7,1.0 Hz,1H),5.27(m,1H),6.78(ddd,J=5.9,2.5,1.7 Hz,1H), 6.90(t,J=2.2 Hz,1H),7.01(m,1H),7.21(t,J=8.1 Hz,1H),7.44 (t,J=7.7 Hz,2H),7.54(m,1H),7.99(m,2H). ^{19}F NMR($CDCl_3$): −106.1(m).

(1S,5R,6R,7R)-2-oxa-7-hydroxy-6-[3,3-difluoro-4-(3-chlorophenoxy)butyl]bicyclo[3.3.0]octan-3-one

^{1}H NMR($CDCl_3$): δ 1.55–1.68(m,2H),1.89(m,1H), 2.1–2.6(m,6H),2.85(dd,J=18.8,11.2 Hz,1H),4.05(m,1H), 4.10(m,2H),4.98(ddd,J=7.1,6.8,2.2 Hz,1H),6.81(ddd,J=8.3, 1.7,1.0 Hz,1H),6.92(t,J=2.2 Hz,1H),7.01(m,1H),7.23(t, J=8.3 Hz,1H). ^{19}F NMR($CDCl_3$): −106.0(m).

EXAMPLE 16

Preparation of 16-(3-chlorophenoxy)-15-deoxy-15, 15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$

The above-identified compound was prepared in the same manner as in Example 6 using 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester prepared in Example 15.

^{1}H NMR($CDCl_3$): δ 1.41(m,2H),1.65–2.40(m,14H),3.95 (m,1H),4.10(t,J=11.6 Hz,2H),4.17(m,1H),5.40(m,2H),6.81 (m,1H),6.92(m,1H),7.00(m,1H),7.22(m,1H). ^{19}F NMR ($CDCl_3$): −105.8(m).

EXAMPLE 17

Preparation of 16-(3-chlorophenoxy)-15-deoxy-15, 15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester

The above-identified compound was prepared in the same manner as in Example 8 using 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ prepared in Example 16.

^{1}H NMR($CDCl_3$): δ 1.42(m,2H),1.7–2.4(m,14H),3.67 (s,3H),3.95(m,1H),4.11(t,J=11.5 Hz,2H),4.20(m,1H),5.41 (m,2H),6.81(m,1H),6.93(m,1H),7.00(m,1H),7.23(m,1H). ^{19}F NMR($CDCl_3$): −105.8(m).

EXAMPLE 18

Preparation of 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester

The above-identified compound was prepared in the same manners as in Examples 1, 14, 2, 3, 4 and 5 using (1S,5R, 6R,7R)-6-formyl-7-benzoyloxy-2-oxabicyclo[3.3.0]octan-3-one and dimethyl 2-oxo-3-phenoxy-propylphosphonate.

^{1}H NMR($CDCl_3$): δ 1.23(d,J=6.4 Hz,6H),1.4–2.5(m, 18H), 3.95(m,1H),4.10–4.94(m,3H),5.00(m,1H),5.42(m, 2H),6.92 (m,2H),7.01(m,1H),7.31(m,2H). ^{19}F NMR ($CDCl_3$): −105.7(m).

The following compounds were prepared in the respective steps in the present Example.

(1S,5R,6R,7R)-2-oxa-7-benzoyloxy-6-(4-phenoxy-3-oxobutyl)bicyclo[3.3.0]octan-3-one

^{1}H NMR($CDCl_3$): δ 1.74(m,2H),2.13(m,1H),2.32–2.52 (m,3H),2.66(m,1H),2.80–2.93(m,3H),4.57(s,2H),5.09(m, 1H), 5.20(m,1H),6.85(d,J=7.8 Hz,2H),6.99(t,J=7.3 Hz,1H), 7.28 (m,2H),7.43(m,2H),7.55(t,J=7.3 Hz,1H),7.98(d,J=7.3 Hz,2H).

(1S,5R,6R,7R)-2-oxa-7-benzoyloxy-6-(3,3-difluoro-4-phenoxybutyl)bicyclo[3.3.0]octan-3-one

^{1}H NMR($CDCl_3$): δ 1.67(m,2H),2.18–2.54(m,6H),2.72 (m,1H),2.94(dd,J=18.3,10.5 Hz,1H),4.13(t,J=11.5 Hz,2H), 5.11 (m,1H),5.26(m,1H),6.89(d,J=7.8 Hz,2H),7.01(t,J=7.3 Hz,1H), 7.30(m,2H),7.44(m,2H),7.56(m,1H),7.99(d,J=7.3 Hz,2H). ^{19}F NMR($CDCl_3$): −105.9(m).

(1S,5R,6R,7R)-2-oxa-7-hydroxy-6-(3,3-difluoro-4-phenoxybutyl)bicyclo[3.3.0]octan-3-one

^{1}H NMR($CDCl_3$); δ 1.47–1.68(m,2H),1.89(m,1H), 2.0–2.2 (m,3H),2.32(dt,J=15.1,5.9 Hz,1H),2.51–2.60(m,2H) ,2.84(dd, J=18.8,11.0 Hz,1H),4.09(m,1H),4.13(t,J=11.5 Hz,2H),4.98 (m,1H),6.92(d,J=8.3 Hz,2H),7.02(t,J=7.3 Hz,1H),7.32(t, J=7.8 Hz,2H). ^{19}F NMR($CDCl_3$): −105.9 (m).

(1S,5R,6R,7R)-2-oxa-3,7-dihydroxy-6-(3,3-difluoro-4-phenoxybutyl)bicyclo[3.3.0]octane

^{1}H NMR($CDCl_3$): δ 1.4–2.5(m,10H),3.95(m,1H),4.12(t, J=11.5 Hz,2H),4.68(m,1H),5.54–5.67(m,1H),6.92(d,J=7.8 Hz, 2H),7.01(t,J=7.3 Hz,1H),7.31(t,J=7.8 Hz,2H). ^{19}F NMR ($CDCl_3$): −105.6(m).

EXAMPLE 19

Preparation of 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$

The above-identified compound was prepared in the same manner as in Example 6 using 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester prepared in Example 18.

^{1}H NMR($CDCl_3$): δ 1.4–2.4(m,18H),3.96(m,1H),4.12(t, J=11.7 Hz,2H),4.17(m,1H),5.40(m,2H),6.92(m,2H),7.00(m, 1H), 7.30(m,2H). ^{19}F NMR($CDCl_3$): −105.7(m).

EXAMPLE 20

Preparation of 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ ethyl ester

The above-identified compound was prepared in the same manner as in Example 7 using 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ prepared in Example 19.

^{1}H NMR($CDCl_3$): δ 1.25(t,J=7.3 Hz,3H),1.4–2.7(m, 18H), 3.95(m,1H),4.09–4.18(m,5H),5.41(m,2H),6.92(m, 2H),7.00 (m,1H),7.30(m,2H). ^{19}F NMR($CDCl_3$): −105.7 (m).

EXAMPLE 21

Preparation of 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester

The above-identified compound was prepared in the same manner as in Example 8 using 16-phenoxy-15-deoxy-15,15-

difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ prepared in Example 19.

^1H NMR($CDCl_3$): δ 1.4–2.6(m,18H),3.66(s,3H),3.95(m, 1H), 4.10–4.19(m,3H),5.41(m,2H),5.76(m,1H),6.92(m,2H), 7.00 (m,1H),7.31(m,2H). ^{19}F NMR($CDCl_3$): −105.7(m).

EXAMPLE 22 (FORMULATION EXAMPLE)

Typical formulations of an ophthalmic solution and an ophthalmic ointment containing 16-phenoxy-15-deoxy-15, 15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester (hereinafter referred to as Compound A) prepared in Example 12 are given below.

1) Ophthalmic Solution 100 ml

Compound A	10 mg
Concentrated glycerine	2500 mg
Polysorbate 80	2000 mg
Sodium dihydrogenphosphate dihydrate	200 mg
Sterilized pure water	appropriate amount
1N hydrochloric acid or 1N sodium hydroxide	appropriate amount
pH	6.0

Based on the above formulation, 0.001% (w/v), 0.005% (w/v), 0.05% (w/v) and 0.1% (w/v) ophthalmic solutions can be prepared by varying the amount of compound A and optionally varying the amounts of the additives.

Moreover, based on the above-formulation, 0.001% (w/v), 0.005% (w/v), 0.01% (w/v), 0.05% (w/v) and 0.1% (w/v) ophthalmic solutions of 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester (hereinafter referred to as Compound B) prepared in Example 8, 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester (hereinafter referred to as Compound C) prepared in Example 21 and 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester (hereinafter referred to as Compound D) prepared in Example 9 can be prepared by using compounds B, C and D instead of compound A and optionally varying the amounts of the additives.

2) Ophthalmic Ointment 100 g

Compound A	0.1 g
Liquid paraffin	20 g
White soft paraffin	77.9 g
Purified lanolin	2 g

Based on the above formulation, similar opthalmic ointments can be prepared by using compounds Br C and D instead of compound A.

The formulation of a ophthalmic solution containing Latanoprost which was used as a comparative compound is shown below.

Ophthalmic solution 100 ml	
Latanoprost	10 mg
Concentrated glycerine	2500 mg
Polysorbate 80	2000 mg
Sodium dihydrogenphosphate dihydrate	200 mg
Sterilized pure water	appropriate amount
1N hydrochloric acid or 1N sodium hydroxide	appropriate amount
pH	6.0

Based on the above formulation, a 0.1% (w/v) ophthalmic solution of Latanoprost can be prepared by varying the amount of Latanoprost and optionally varying the amounts of the additives.

EXAMPLE 23 (PHARMACOLOGICAL TESTS)

The effects of compounds of the present invention on intraocular pressure and melanogenesis were investigated to find their usefulness as medicines for an ocular disease. Eye irritations caused by them were assessed in accordance with the method of Fukui et al. ("Gendai-no-rinsho", Vol. 4, 277–289 (1970)), and they were found to be irritant to the eye as little as Latanoprost.

1) Effects on Intraocular Pressure

The effects of single application and two-week repeated application of compounds of the present invention to the eye were studied in accordance with the method disclosed in a report of a study on the effect of the tromethamine salt and the isopropyl ester of $PGF_{2\alpha}$ on intraocular pressure in crab-eating macaques (Exp. Eye Res., 61, 677–683 (1995)).

(a) Single Application Test

(Method)

Crab-eating macaques weighing from 2.5 to 7.5 kg (3–10 years old) were used in the test. The intraocular pressures were measured just before and 4, 6 and 8 hours after application of the test compounds under ketamine anesthasia (5–10 mg/kg, intramuscular administration) by means of an air-puff applanation tonometer.

(Results)

Table 1 shows the resulting changes in intraocular pressure with time after application of 20 μl of 0.01% (w/v) and 0.1% (w/v) ophthalmic solutions containing compounds A, B, C or D, in relation to the initial intraocular pressure (the intraocular pressure just before application). The results of application of 0.01% (w/v) and 0.1% (w/v) ophthalmic solutions containing Latanoprost, which is known as a therapeutic agent for glaucoma are also shown in Table 1. In the square brackets are the numbers of subjects.

TABLE 1

			Change in ocular pressure after application (mmHg)		
			4 hours	6 hours	8 hours
Compound A	(0.01%)	[7]	−1.7	−2.3	−2.3
	(0.1%)	[8]	−2.6	−3.0	−3.1
Compound B	(0.01%)	[10]	−0.9	−1.0	−1.0
	(0.1%)	[9]	−1.3	−1.4	−2.0
Compound C	(0.01%)	[9]	−0.6	−1.2	−2.0
	(0.1%)	[9]	−1.0	−0.4	−2.0
Compound D	(0.01%)	[12]	−0.1	−0.8	−1.3
	(0.1%)	[12]	−0.8	−1.6	−2.3
Latanoprost	(0.01%)	[5]	−0.4	−1.2	−0.6
	(0.1%)	[8]	−0.8	−1.3	−0.8

As is evident from Table 1, the intraocular pressure had already started to decrease 4 hours after the application of compounds of the present invention and was still decreasing even 8 hours after the application. Compound A lowered the intraocular pressure twice as much as Latanoprost did 6 hours after application, and about 4 times as much 8 hours after application.

This proves that the compound of the present invention has a long-lasting effect of lowering intraocular pressure.

(b) Two-week Repeated Application Test

(Method)

Crab-eating macaques weighing from 2.4 to 5.6 kg (3 to 8 years old) were used in the test. A 20 μl of a test ophthalmic solution was applied to one of the eyes of each macaque, and an equal volume of the corresponding vehicle solution (which was of the same formulation as the ophthalmic solution containing the test compound but did not contain the test compound) was applied to the other eye once a day

for 14 consecutive days. The intraocular pressure was measured under ketamine anesthasia (5–10 mg/kg, intramuscular administration) by means of an air-puff applanation tonometer.

(Results)

Table 2 illustrates the resulting difference in intraocular pressure between the right and left eyes [(the intraocular pressure of an eye treated with an ophthalmic solution containing a test compound)—(the intraocular pressure of an eye treated with the corresponding vehicle solution)] 6 hours after application of a 0.01% (w/v) or 0.1% (w/v) ophthalmic solution containing compound D or a 0.1% (w/v) ophthalmic solution containing compound A or B on the 1st, 3rd, 7th, 10th and 14th days. The results of application of a 0.1% (w/v) ophthalmic solution containing Latanoprost, which is known as a therapeutic medicine for glaucoma are also shown in Table 2. In the square brackets are the numbers of subjects.

TABLE 2

			Difference in intraocular pressure between the right and left eyes (mmHg) [(Intraocular pressure of the eye treated with test compound) − (Intraocular pressure of the eye treated with vehicle solution)]				
			1st day	3rd day	7th day	10th day	14th day
Compound A	(0.1%)	[7]	−0.5	−2.7	−3.4	−3.3	−2.6
Compound B	(0.1%)	[7]	−0.5	−2.5	−3.2	−2.8	−1.9
Compound D	(0.01%)	[7]	−2.1	−2.8	−3.0	−2.2	−1.9
	(0.1%)	[7]	−1.6	−4.4	−3.9	−2.7	−2.4
Latanoprost	(0.1%)	[7]	−0.6	−2.1	−1.7	−0.7	−0.3

As is evident from Table 2, the intraocular pressure had remarkably decreased since the 3rd day from the start of the application of compounds of the present invention and kept low till the 14th day. Compound D lowered intraocular pressure about 2 to 8 times as much as Latanoprost did. When the intraocular pressures were measured, no turbid cornea, abnormal conjunctiva vessels, conjunctivoma or secretions were observed.

This proves that the compound of the present invention has an excellent effect of lowering intraocular pressure.

2) Effects on Melanogenesis

The effect of compounds of the present invention on melanogenesis was investigated by using B16 pigment cells in accordance with a report of a study on the effect of pyrroloquinoline quinone on expression of mRNA of tyrosinase, which is involved in melanogenesis (Life Sci., 56, 1707–1713 (1995)).

(Method)

To a B16 pigment cell culture (2×10^3 cells/ml) preincubated at 37° C. under 5% CO_2 for 24 hours, a test compound was added, and the culture was incubated at 37° C. under 5% CO_2 for 48 hours. After renewal of the culture medium and addition of the test compound, the cell culture was incubated at 37° C. under 5% CO_2 for another 48 hours. The B16 pigment cells were separated from the culture medium and dissolved in a 0.1N sodium hydroxide- 10% triton-X mixed solution, and the absorbances of the culture medium and the cell solution (wavelength 415 nm) were measured.

The gross amounts of melanin in the culture medium and the cell solution were determined from a calibration chart prepared by using synthetic melanin standard solutions. The amount of protein in the culture medium was measured, and the melanin content was given by the following equation and represented in relation to the amount of melanin in the absence of the test compound.

$$\text{Melanin content (\%)} = \frac{(A_s + B_s)/P_s}{(A_c + B_c)/P_c} \times 100$$

A_c: Absorbance of the culture medium in the absence of a test compound

B_c: Absorbance of cell solution in the absence of a test compound

P_c: The amount of protein in a cell solution in the absence of a test compound

A_s: Absorbance of the culture medium in the presence of a test compound

B_s: Absorbance of the cell solution in the presence of a test compound

P_s: The amount of protein in the cell solution in the presence of a test compound

(Results)

Table 3 illustrates the effect of addition of the free forms (carboxylic acids) of Compounds A, B and C on melanogenesis by B16 pigment cells. The results of addition of the free form (a carboxylic acid) of Latanoprost, which is known as a therapeutic medicine for glaucoma are also shown in Table 3. The free form of Compound D is the same as that of Compound A.

TABLE 3

	Concentration		
	1 μM	10 μM	100 μM
Compound A	102%	113%	111%
Compound B	110%	122%	107%
Compound C	107%	116%	127%
Latanoprost	109%	136%	224%

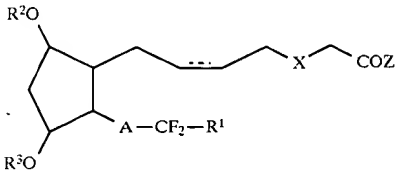
As is evident from Table 3, compounds of the present invention did not have much effect and, the melanin contents in the presence of 100 μM of them were only about 1.1 to 1.3 times higher than that in the absence of them. On the other hand, when Latanoprost was added at concentrations of 10 μM and 100 μM, the melanin contents were about 1.4 times and about 2.2 times, respectively, higher than that in its absence.

This proves that compounds of the present invention have little effect on melanogenesis and do not cause iridal pigmentation when applied repeatedly.

The results of the pharmacological tests clearly indicate that the compounds of the present invention are useful as long-lasting therapeutic medicines for glaucoma, are hardly irritant to the eye and have little effect on melanogenesis.

What is claimed is:

1. A fluorine-containing prostaglandin derivative of the following formula (1) or a salt thereof:



(1)

wherein A is an ethylene group, a vinylene group, an ethynylene group, —OCH_2— or —SCH_2—,

R^1 is a substituted or unsubstituted aryloxyalkyl group,

each of R^2 and R^3 which are independent of each other, is a hydrogen atom or an acyl group, or forms a single bond together with Z,

X is —CH_2—, —O— or —S—,

Z is —OR^4, —$NHCOR^5$, —$NHSO_2R^6$ or —SR^7, or forms a single bond together with R^2 or R^3,

each of R^4, R^5, R^6 and R^7 which are independent of one another, is a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an aryl group or an aralkyl group,

and a dual line consisting of solid and broken lines is a single bond, a cis-double bond or a trans-double bond.

2. The compound according to claim **1**, wherein R^1 is a phenoxymethyl group, a 3,5-dichlorophenoxymethyl group or a 3-chlorophenoxymethyl group.

3. The compound according to claim **1**, which is 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ or an alkyl ester or a salt thereof.

4. A medicine containing the compound according to claim **1** as an active ingredient.

5. The medicine according to claim **4**, which is a preventive or therapeutic medicine for an eye disease.

6. The medicine according to claim **5**, wherein the eye disease is glaucoma or ocular hypertension.

7. The medicine according to claim **4**, **5** or **6**, wherein A is an ethylene group or a vinylene group.

8. The medicine according to claim **4**, **5** or **6**, wherein X is —CH_2—.

9. The medicine according to claim **4**, **5** or **6**, wherein both R^2 and R^3 are hydrogen atoms.

10. The medicine according to claim **4**, **5** or **6**, wherein Z is —OR^4.

11. The medicine according to claim **9**, wherein R^1 is a phenoxymethyl group, a 3,5-dichlorophenoxymethyl group or a 3-chlorophenoxymethyl group.

12. A medicine containing 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ or an alkyl ester or salt thereof as an active ingredient.

13. The medicine according to claim **12**, which is a preventive or therapeutic medicine for an eye disease.

14. The medicine according to claim **13**, wherein the eye disease is glaucoma or ocular hypertension.

* * * * *

Return To:

USPTO Home Page

Finance Online Shopping Page

United States Patent and Trademark Office

ATTACHMENT C

Maintenance Fee Statement

03/09/2012 01:26 PM EST

Patent Number: 5886035

Customer Number: 22850

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTA
1940 DUKE STREET
ALEXANDRIA VA 22314

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,886,035	$4,110.00	$0.00	08/26/10	08/993,017	03/23/99	12/18/97	12	NO	ASAHI GLASS COMPANY LTD E

Click here to obtain your Maintenance Fee Statement as a PDF.
Please note that in order to view your Maintenance Fee Statement as a PDF, you must have Adobe's Acrobat Reader installed. If you do not have it, download it for FREE!

Get Acrobat Reader

ATTACHMENT C

United States Patent and Trademark Office

Patent Bibliographic Data				03/09/2012 01:17 PM	
Patent Number:	5886035		**Application Number:**	08993017	
Issue Date:	03/23/1999		**Filing Date:**	12/18/1997	
Title:	DIFLUOROPROSTAGLANDIN DERIVATIVES AND THEIR USE				
Status:	4th, 8th and 12th year fees paid			**Entity:**	Large
Window Opens:	N/A	**Surcharge Date:**	N/A	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	08/26/2010 09/01/2006 08/29/2002 06/10/1999	Payment of Maintenance Fee, 12th Year, Large Entity. Payment of Maintenance Fee, 8th Year, Large Entity. Payment of Maintenance Fee, 4th Year, Large Entity. Payor Number Assigned. --- End of Maintenance History ---			
Address for fee purposes:	OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTA 1940 DUKE STREET ALEXANDRIA VA 22314				

Run Another Query

Need Help? | USPTO Home Page | Finance Online Shopping Page | Alerts Page

ATTACHMENT D

Compound ID	Project Name	Application Type	Qualifier	Prefix	Reg#	Serial #	Supplement #	eCTD	ShortDescription	LongDescription	FileDate
2452		IND/BBIND	IND/BBIND - Original	IND	62,690	0		No	Initial Filing	Santen Incorporated Notice of Claimed Investigational Exemption (IND) AFP-168 Topical Ophthalmic Drug Product (prostaglandin F2a analogue) for the treatment of elevated intraocular pressure (IOP) associated with open-angle glaucoma or ocular hypertension	5/23/2001 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	FDA comments regarding May 25, 2001 submission		6/28/2001 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	1		No	Request for Carcinogenicity Waiver Amendment 001	Requesting Carcinogenicity Waiver under Nonclinical Pharmacology and Toxicology requirements	7/3/2001 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	FDA Chemist's Comments regarding May 23, 2001 submission		7/27/2001 0:00
2452		IND/BBIND	Response to Agency	IND	62,690	2		No	Response to Comments Received from FDA Clinical Reviewer	Request for FDA Comments on Clinical Study Design: Requirement for BID Study	8/9/2001 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	4		No	Additional Signed Form 1572 and Investigator Curricula Vitae, Study WW-15-001-US	This amendment updates the investigator information for the Phase II clinical study namely, Study WW-15-001-US and includes the following additional investigator curriculam vitae and signed Form 1572s: 1. David G. Shulman, M.D â€¢ Jay M. Rubin, M.D 2. Thomas Mundorf, M.D 3. Stephen B.Whiteside, M.D	9/6/2001 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Fax of cover letter from serial no. 4 sent to Mike Puglisi		9/6/2001 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	FDA Comments regarding Serial no. 0002 submitted on August 9, 2001		9/25/2001 0:00
2452		IND/BBIND	Response to Agency	IND	62,690	5		No	Response to Comments Received from FDA Chemistry Reviewer	Amendment provides responses to comments received from the FDA chemist as provided by Mike Puglisi on July 27, 2001	10/5/2001 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	6		No	Additional Signed Form 1572 and Investigator CVs, Study WW-15-001-US	This amendment updates the investigator information for the Phase II clinical study namely, Study WW-15-001-US and includes the following additional investigator curriculam vitae and signed Form 1572s: 1. Thomas Walters, MD â€¢ Douglas Lewis, MD 2. Richard Evans, MD â€¢ Jorge De La Chapa, DO 3. Steven Mansberger, MD â€¢ George Cioffi, MD	10/11/2001 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Fax sent to Ms. Lori Gorski with a Copy of September 25, 2001 fax		11/26/2001 0:00

2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	8		No	Additional Signed Form 1572 and Investigator CVs, Study WW-15-001-US	This amendment updates the investigator information for the Phase II clinical study namely, Study WW-15-001-US and includes the following additional investigator curriculam vitae and signed Form 1572s: 1. H. Jerome Cramptom, MD â€¢ Gerald P. Spindel, MD â€¢ Terry L.N. Chin, O.D. â€¢ Timothy W. Jordan, O.D. â€¢ Douglas J. Blair, O.D. â€¢ Jack V. Greiner, D.O., Ph.D. â€¢ Charles Leahy, O.D. â€¢ Amy Catherine Nau, O.D. 2. Steven Mansberger, MD (updated 1572 only) 3. Thomas R. Walters, M.D. â€¢ James E. Montgomery 4. Stephen Whiteside, M.D. â€¢ Douglas Lewis, M.D. 5. James Montgomery, M.D. â€¢ Thomas Walters, M.D. 6. David G. Shulman, M.D. (updated 1572 only)	3/28/2002 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	9		No	Additional Signed Form 1572 and Investigator CVs, Study WW-15-001-US	This amendment updates the investigator information for the Phase II clinical study namely, Study WW-15-001-US and includes the following additional investigator curriculam vitae and signed Form 1572s: 1. H. Jerome Crampton, M.D. (Updated 1572 only) â€¢ Mark Latina, M.D. (New sub-investigator) 2. Clifford Michaelson, MD (New principal investigator) â€¢ H. Jerome Crampton, MD (Updated 1572 only)	4/30/2002 0:00
2452		IND/BBIND	Annual Report	IND	62,690	10		No	Report Period: June 30, 2001 through June 29, 2002		8/29/2002 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Protocol	IND	62,690	11		No	New Protocol: Study 15-002 and updated investigator's brochure	Protocol update for the Phase 2b clinical trial to support the approval of AFP-168 ophthalmic solution in lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension, along with an updated investigator's brochure	12/4/2002 0:00
2452		IND/BBIND	IND/BBIND - Amendment - CMC	IND	62,690	12		No	CMC update for the Phase 2b clinical trial		12/27/2002 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	13		No	Request for teleconference	Request for teleconference to discuss Phase 3 Study design	3/25/2003 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	FDA meeting minutes from 3/31/03 teleconference		5/13/2003 0:00
2452		IND/BBIND	Annual Report	IND	62,690	14		No	Report Period: June 30, 2002 through June 29, 2003		8/8/2003 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	15		No	Official Request for an End-of-Phase 2 Meeting	Official request for an End-of-Phase 2 meeting to discuss the results from our recently completed Phase 2 clinical study and to confirm plans for a Phase 3 program to support approval of 0.0015% AFP-168 Ophthalmic Solution for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.	9/8/2003 0:00

2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Official Request for an End-of-Phase 2 Meeting		9/8/2003 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	16		No	Withdrawal of Official Request for an End-of-Phase 2 Meeting		10/8/2003 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Protocol	IND	62,690	17		No	New Protocol: Study 15-003 and updated investigator's brochure	Protocol update for the Phase 3 clinical trial to support the international development of AFP-168 ophthalmic solution in lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension, along with an updated investigator's brochure	6/10/2004 0:00
2452		IND/BBIND	IND/BBIND - Amendment - CMC	IND	62,690	18		No	CMC update for the Phase 3 clinical trial		6/30/2004 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	19		No	Additional Signed Form 1572s and Investigator Curricula Vitae, Study WW-15-003-US	This amendment updates the investigator information for the Phase 3 clinical trial namely, Study WW-15-003-US and includes the following additional investigator curriculam vitae and signed Form 1572s: 1. Jason Bacharach, M.D. â€¢ William H. Bartlett, M.D. 2. H. Jerome Crampton, MD â€¢ Gail Torkildsen, MD â€¢ Terry Chin, OD 3. Douglas G. Day, MD 4. Richard M. Evans, MD â€¢ Jason D. Burns, M.D. 5. Thomas K. Mundorf, MD 6. Bernard R. Perez, MD â€¢ Don J. Perez Ortiz, MD 7. Kenneth Neill Sall, MD 8. Elizabeth D. Sharpe, MD 9. O. Dara Stevenson, MD 10. Michael E. Tepedino, MD 11. Thomas R. Walters, MD â€¢ Douglas E. Lewis, MD	7/8/2004 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	20		No	Additional Signed Form 1572s and Investigator Curricula Vitae, Study WW-15-003-US	This amendment updates the investigator information for the Phase 3 clinical trial namely, Study WW-15-003-US and includes the following additional investigator curriculam vitae and signed Form 1572s: 1. Alan E. Jackson, M.D. â€¢ Steven T. Jackson, M.D. â€¢ Mike Kenneth Mitchell, O.D. 2. John E. Bokosky, MD â€¢ Neil T. Choplin, MD â€¢ Philip M. Taunton, OD 3. John J. Alpar, MD â€¢ Andrew J. Alpar, D.O 4. Joseph L. Sokol, MD 5. Juan Orellana, MD 6. Kenneth W. Olander, MD 7. Robert D. Williams, MD â€¢ James D. Hurt, OD	8/5/2004 0:00
2452		IND/BBIND	Annual Report	IND	62,690	21		No	Report Period: June 30, 2003 through June 29, 2004		8/13/2004 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	22		No	Additional Signed Form 1572s and Investigator Curricula Vitae, Study WW-15-003-US	This amendment updates the investigator information for the Phase 3 clinical trial namely, Study WW-15-003-US and includes the following additional investigator curriculam vitae and signed Form 1572: Yue-Kong Au, MD	9/2/2004 0:00

2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	23		No	Additional Signed Form 1572s and Investigator Curricula Vitae, Study WW-15-003-US	This amendment updates the investigator information for the Phase 3 clinical trial namely, Study WW-15-003-US and includes the following additional investigator curriculam vitae and signed Form 1572s: 1. Alfred M. Solish, M.D. â€¢ Margaret S. Good, M.D. 2. Gail F. Schwartz, MD â€¢ Raya Armaly, MD 3. Stephen B. Whiteside, MD â€¢ Mark S. Foster, MD 4. H. Jerome Crampton, MD 5. Eugene E. Protzko, MD â€¢ Christina P. Pellegrino, O.D. 6. Elizabeth D. Sharpe, MD 7. Thomas R. Walters, MD â€¢ Robert E Marquis, MD â€¢ Kristin A. Sargent, MD	9/30/2004 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	Clinical Comments re: 6/10/04 Amendment		10/6/2004 0:00
2452		IND/BBIND	IND/BBIND - Amendment - Change Protocol	IND	62,690	24		No	Protocol: 15-003	Protocol update for the Phase 3 clinical trial to support the international development of AFP-168 ophthalmic solution in lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension	10/8/2004 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Fax to Mike Puglisi of Cover letter and first two pages of amended protocol 15-003		10/8/2004 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Copy of Protocol 15-003 sent to Mike Pugligi through email		10/8/2004 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	25		No	Additional Signed Form 1572s and Investigator Curricula Vitae, Study WW-15-003-US	This amendment updates the investigator information for the Phase 3 clinical trial namely, Study WW-15-003-US and includes the following additional investigator curriculam vitae and signed Form 1572s: Eugene E. Protzko, MD â€¢ David D. Reed, O.D. â€¢ Scott M. Smearman, OD	10/28/2004 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	26		No	Additional Signed Form 1572s and Investigator Curricula Vitae, Study WW-15-003-US	This amendment updates the investigator information for the Phase 3 clinical trial namely, Study WW-15-003-US and includes the following additional investigator curriculam vitae and signed Form 1572s: 1. Stacey L. Ackerman, M.D. â€¢ Joseph I. Markoff, M.D. â€¢ Robert D. Behar, MD â€¢ Marc D. Garden, MD â€¢ Mark H. Blecher, M.D. â€¢ Carolyn S. Repke, MD 2. Moiz M. Carim, MD â€¢ Glen S. Corbin, OD â€¢ Darrin A. Rich, OD â€¢ Robert A. Copeland, OD â€¢ Nicole M. Forney, OD â€¢ Leah R. Wartluft, MD	11/24/2004 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Cover Letter for Serial No. 0027 faxed to Mike Puglisi		12/21/2004 0:00

2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	27		No	Additional Signed Form 1572s and Investigator Curricula Vitae, Study WW-15-003-US	This amendment updates the investigator information for the Phase 3 clinical trial namely, Study WW-15-003-US and includes the following additional investigator curriculam vitae and signed Form 1572: Kenneth Sall, MD	12/21/2004 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Cover Letter for Serial No. 0028 faxed to Mike Puglisi		1/19/2005 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	28		No	Additional Signed Form 1572s and Investigator Curricula Vitae, Study WW-15-003-US	This amendment updates the investigator information for the Phase 3 clinical trial namely, Study WW-15-003-US and includes the following additional investigator curriculam vitae and signed Form 1572: Gail F. Schwartz, MD	1/19/2005 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Fax to Mike Puglisi of AEs sent to agency on Jan-27-2005		1/27/2005 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Protocol	IND	62,690	30		No	New Protocol: Study 15-005	Protocol update for a pharmacokinetic clinical trial to support the international development of AFP-168 ophthalmic solution in lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension	4/22/2005 0:00
2452		IND/BBIND	Annual Report	IND	62,690	31		No	Report Period: June 30, 2004 through June 29, 2005		8/15/2005 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	32		No	Request for Scientific Consultation		8/16/2005 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Fax sent to Miki Puglisi of cover letter for scientific consultation meeting		8/16/2005 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	33		No	Briefing package for Scientific Consultation	Consultation scheduled for October 12, 2005 from 11am to 12pm	9/16/2005 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Desk copies serial no. 033 sent to Mike Puglisi		9/16/2005 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Fax sent to Mike Puglisi of serial No. 034		9/29/2005 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	Answers to 10/12 2005 Meeting questions		10/6/2005 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	Attendees for October 12, 2005 meeting		10/12/2005 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	35		No	Scientific consultation meeting minutes	Meeting minutes from October 12, 2005 scientific consulation meeting	10/21/2005 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Cover letter of Scientific consultation meeting minutes faxed to Mike Puglisi		10/21/2005 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	FDA meeting minutes from October 12, 2005 Scientific meeting		11/2/2005 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	36		No	Additional Signed Form 1572s and Investigator Curricula Vitae, Study WW-15-003-US	This amendment updates the investigator information for the Phase 3 clinical trial namely, Study WW-15-003-US and includes the following additional investigator curriculam vitae and signed Form 1572s: 1. Moiz Carim, M.D. 2. Alfred Solish, MD 3. O. Dara Stevenson, MD 4. Stephen Whiteside, MD	2/22/2006 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Copy of Serial no. 036 faxed to Mike Puglisi (Cover Letter only)		2/22/2006 0:00

2452		IND/BBIND	Annual Report	IND	62,690	38		No	Report Period: June 30, 2005 through June 29, 2006		8/11/2006 0:00
2452		IND/BBIND	Annual Report	IND	62,690	39		No	Report Period: June 30, 2006 through June 29, 2007		8/17/2007 0:00
2452		IND/BBIND	Annual Report	IND	62,690	40		No	Report Period: June 30, 2007 through June 29, 2008		8/5/2008 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	NA		No	Santen names Merck as Agent for IND	Santen names Merck as Agent for IND 62,690	5/28/2009 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	41		Yes	Request for Type B End of Phase II FDA Meeting	Request for Type B End of Phase II FDA Meeting	6/3/2009 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	FDA email confirmation of August 24, 2009 End of Phase II Meeting	FDA email confirmation of August 24, 2009 End of Phase II Meeting - no fax or letter was received - the email is the official confirmation	6/12/2009 0:00
2452		IND/BBIND	IND/BBIND - Amendment - Pharmacology/Toxicology	IND	62,690	42		Yes	Three Santen preclinical safety reports	Three Santen preclinical safety reports - these reports were not previously submitted to FDA by Santen	7/14/2009 0:00
2452		Agency Mtg& Advice Proc	Background Package - Agency	IND	62,690	NA		Yes	August 24, 2009 End-of-Phase II meeting background package	Merck Research Laboratories (MRL) is providing a background package for Agency review, in support of the August 24, 2009 End-of-Phase II meeting.	7/23/2009 0:00
2452		IND/BBIND	IND/BBIND - Amendment - Clinical	IND	62,690	44		Yes	Edition 8 of CIB	Edition 8 of CIB - note that Edition 7 was never submitted because Edition 8 was completed shortly after Edition 7.	8/5/2009 0:00
2452		IND/BBIND	IND/BBIND - Amendment - Pharmacology/Toxicology	IND	62,690	46		Yes	Nonclinical Study Reports		8/13/2009 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	FDA fax containing preliminary comments on End of Ph II Meeting questions	FDA fax containing prelimiary comments of the questions asked in the background package for the End of Phase II Meeting	8/18/2009 0:00
2452		IND/BBIND	Annual Report	IND	62,690	47		Yes	Ophthalmic Solution Annual Report for 30-Jun-2008 through 29-Jun-2009.		8/21/2009 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	48		Yes	MRL Minutes of August 24, 2009 End of Phase II Meeting	MRL Minutes of August 24, 2009 Type II End of Phase II Meeting with FDA	9/9/2009 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	Meeting minutes from EoP Meeting w/FDA for MK-2452.	FDA's Official Meeting minutes from EoP Meeting w/FDA for MK-2452 on August 24, 2009.	9/23/2009 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	50		No	Santen Letter to FDA Transfer of IND	Copy of letter submitted by Santen to FDA, which informed FDA that the IND was being transferred to Merck, effective immediately.	11/12/2009 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	51		Yes	Transfer of IND from Santen to Merck; Transfer of responsibility to Chitkala Kalidas	Transfer of IND from Santen to Merck, in response to Santen's letter to the FDA informing them of the change of sponsorship; Transfer of responsibility to Chitkala Kalidas	11/23/2009 0:00
2452		IND/BBIND	IND/BBIND - Amendment - CMC	IND	62,690	52		Yes	Amendment to provide MK-2452 Drug Substance, Product, Placebo and Comparator for PN 001	Amendment to provide MK-2452 Drug Substance, Drug Product, Placebo Information and Timolol Maleate Comparator for PN 001	11/30/2009 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Protocol	IND	62,690	53		Yes	Original Phase III Protocol 001-01	Original Protocol 001-01 (PN001-00 was never submitted)	12/2/2009 0:00
2452		IND/BBIND	IND/BBIND - Amendment - Clinical	IND	62,690	54		Yes	CIB Edition 9	CIB Edition 9, dated Nov. 12, 2009	12/2/2009 0:00

2452		IND/BBIND	IND/BBIND - Amendment - Clinical	IND	62,690	55		Yes	Notice of CRO transfer of sponsor obligations	Notice of CRO transfer of sponsor obligations to Perceptive Informatics, Inc. for IVRS function	12/18/2009 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	56		Yes	New Investigators for PN 001	New Investigators for PN 001 - 13 investigators	1/15/2010 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	58		Yes	13 New PIs for Protocol 001-01	13 New PIs for Protocol 001-01	2/25/2010 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	FDA letter providing comments for Protocol 001	FDA letter providing comments for Protocol 001: 1. Submit PI qualifications prior to their enrolling patients 2. Recommendation of comparison between PF tafluprots, PC tafluprost adn PF timolol 3. Statistical adjustment for interim analysis is not required	2/26/2010 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	60		Yes	7 New Investigators for Protocol 001-01	7 New Investigators for Protocol 001-01 - Berlin, Khaimi, Miller-Ellis, Noecker, Sokol, Barnebey, Peace	3/16/2010 0:00
2452		IND/BBIND	Response to Agency	IND	62,690	62		Yes	Response to FDA fax of February 26, 2010	Response to FDA fax of February 26, 2010 which contained the FDA clinical reviewers comments regarding Protocol 001-01.	3/26/2010 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	63		Yes	Submission of Datasets, Define file and CRFs as discussed in March 15, 2010 email	Submission of Datasets, Define file and CRFs for Protocol 001 that will be included in NDA, as discussed in March 15, 2010 email	3/26/2010 0:00
2452		IND/BBIND	IND/BBIND - Amendment - New Investigator	IND	62,690	65		Yes	Three New Investigators for Protocol 001-02	Three New Investigators for Protocol 001-02 Felipe A. Medeiros, M.D. - Rohit Varma, M.D.- Marshall N. Cyrlin, M.D.	4/14/2010 0:00
2452		IND/BBIND	IND/BBIND - Original	IND	62,690	66		Yes	Type B Pre NDA Meeting Request	Pre NDA Meeting Request for a Type B meting to discuss details of the NDA submission.. Target is June 2010.	4/20/2010 0:00
2452		IND/BBIND	IND/BBIND - Amendment - Change Protocol	IND	62,690	68		Yes	Protocol Amendment 001-02	Protocol Amendment 001-02	4/26/2010 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	FDA Letter granting Pre NDA Meeting on August 13, 2010	FDA Letter granting Pre NDA Meeting on August 13, 2010 to discuss the NDA filing for Tafluprost PF.	5/11/2010 0:00
2452		IND/BBIND	IND/BBIND - Amendment - Clinical	IND	62,690	74		Yes	Additional Site Address for Dr. Miller-Ellis	Additional Site Address for Dr. Miller-Ellis - Box 3 1571 form.	5/24/2010 0:00
2452		Agency Mtg& Advice Proc	Agency correspondence (general) - Outgoing					No	Request for Pre IND Meeting for Tafluprost Fixed Dose Combinations	Request for Pre IND Meeting for Tafluprost Fixed Dose Combinations - no MK numbers or Pre IND numbers are assigned at this time for double and triple combinations. The edossier posting will be under MK-2452 until such time as a Pre IND number is assigned.	6/21/2010 0:00
2452		Agency Mtg& Advice Proc	Background Package - Agency	IND	62,690	85		Yes	Tafluprost MK-2452 Pre NDA Mtg Background Pkg	Tafluprost MK-2452 Pre NDA Mtg Background Pkg	7/8/2010 0:00
2452		IND/BBIND	Agency correspondence - Incoming					No	FDA letter assigning Pre IND number to tafluprost fixed dose combination	FDA letter assigning Pre IND number 109,172 to tafluprost fixed dose double and triple combinations	7/9/2010 0:00

2452		IND/BBIND	Agency correspondence - Incoming					No	FDA letter confirming Pre IND meeting for October 22, 2010	FDA letter confirming Pre IND meeting for October 22, 2010 to discuss developmental program for tafluprost fixed dose double and triple combinations	7/13/2010 0:00
2452		IND/BBIND	Annual Report	IND	62,690	87		Yes	Ophthalmic Solution Annual Report for 30-Jun-2009 through 29-Jun-2010.		8/13/2010 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	90		Yes	Request for Proprietary Name Review	Request for Proprietary Name Review of SAFLUTAN as the US trademark for tafluprost.	9/30/2010 0:00
2452		Agency Mtg& Advice Proc	Agency correspondence - Incoming	IND	62,690	NA		No	FDA Version of August 13, 2010 pre-NDA Meeting Minutes	FDA sent formal meeting minutes for the Pre-NDA meeting on August 13, 2010	9/30/2010 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	91		Yes	Merck Minutes of FDA Pre-NDA meeting of Aug 13, 2010	Merck Minutes of FDA Pre-NDA meeting of Aug 13, 2010 to discuss the upcoming NDA for tafluprost	10/1/2010 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	94		Yes	Sample Statistical Review Aid packages in three different formats	Sample Statistical Review Aid packages in three different formats for all Phase II and III studies in US, EU and Japan, as requested by FDA at the Pre NDA meeting of Aug 13, 2010.	11/30/2010 0:00
2452		Marketing Application	Agency correspondence (general) - Outgoing	NDA	202-514		NA	No	User Fee for Original NDA 202-514	User Fee for NDA 202-514 sent to Wells Fargo for original NDA to be submitted Jan 7, 2011	12/14/2010 0:00
2452		Marketing	Marketing application - Original	NDA	202-514		NA	Yes	Original Preservative Free NDA	Original Preservative Free NDA US - FDA	1/7/2011 0:00
2452		Marketing Application	Marketing Application - Amendment to Pending	NDA	202-514		NA	Yes	AMENDMENT TO A PENDING APPLICATION - FINANCIAL DISCLOSURE	AMENDMENT TO A PENDING APPLICATION FINANCIAL DISCLOSURE Reference is made to the MK-2452 New Drug Application.	1/7/2011 0:00
2452		Marketing Application	Marketing Application - Amendment to Pending	NDA	202-514		NA	Yes	AMENDMENT TO A PENDING APPLICATION - FINANCIAL DISCLOSURE SANTEN, INC. STUDIES	AMENDMENT TO A PENDING APPLICATION FINANCIAL DISCLOSURE â€" SANTEN, INC. STUDIES Reference is made to the MK-2452 New Drug Application.	1/7/2011 0:00
2452		IND/BBIND	Agency correspondence (general) - Outgoing	IND	62,690	100		Yes	Withdrawal of Request for Proprietary Name Review	Withdrawal of Request for Proprietary Name Review letter which was submitted on Sept 30, 2010. The request for name review is being submitted to the NDA as per Agency request.	1/20/2011 0:00
2452		Marketing Application	Agency correspondence (general) - Outgoing	NDA	202-514		NA	Yes	Request for expedited review of proprietary name SAFLUTAN	Request for expedited review of proprietary name SAFLUTAN. Per Agency request, the letter to the IND for tradename review was withdrawn and with this submission, is being sent to the NDA.	1/20/2011 0:00
2452		Marketing Application	Agency correspondence - Incoming	NDA	202-514		NA	No	FDA Request for information for NDA 202514	FDA Request for CMC Information submitted in DMF 24400	2/3/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Response to FDA for CMC information related to DMF 24400 for drug substance.	Response to FDA for CMC information related to DMF 24400 for drug substance, Modules 2.3.S and 3.2.S, as requested in a Jan 28, 2011 FDA letter.	2/9/2011 0:00
2452	SAFLUTAN	Marketing Application	Agency correspondence - Incoming	NDA	202-514		NA	No	NDA Acknowledgement Letter for Tafluprost (MK-2452)	Formal letter from the FDA acknowledging receipt of the NDA for tafluprost	2/15/2011 0:00

2452		Marketing Application	Marketing Application - Amendment to Pending	NDA	202-514		NA	Yes	Revised Patient Package Insert	This amendment provides changes to the PPI that was submitted as part of the original NDA.	2/17/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Response to FDA Request for listing of Patients receiving PF tafluprost or timolol	Response to FDA Request to provide the number of subjects randomized to preservative-free tafluprost or preservative-free timolol at each investigational site for Protocol 001	2/28/2011 0:00
2452		IND/BBIND	Agency correspondence - Incoming	IND	62,690	NA		No	FDA Letter confirming withdrawal of tradename submitted to IND	Formal letter from the FDA confirming withdrawal of the tradename (Saflutan) review request submitted to tafluprost IND (IND 62690)	3/9/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Response to FDA request regarding DMEPA, DSI and Statistical Information	Response to FDA request regarding DMEPA, DSI and Statistical Information; the CMC portion of the same FDA request will be submitted at a later date.	3/23/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Response to FDA questions received on March 7, 2011 regarding Microbiology (sterility)	Response to FDA questions received on March 7, 2011 regarding Microbiology (sterility). The first part of this response was submitted on March 23, 2011.	3/29/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Integrated Datasets and Programs in Response to March 5, 2011 FDA Request	Response to Question #7/Statistical Information of March 7, 2011 email request for integrated datasets and the programs used to conduct the analyses according to the integrated SAP for the ISE and ISS reports.	4/4/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Response to FDA Query #5 of March 7, 2011 FDA Request	Response to FDA Query #5 of March 7, 2011 FDA Request for site-level datasets for Protocol 001.	4/6/2011 0:00
2452		IND/BBIND	IND/BBIND - Amendment - Clinical	IND	62,690	109		Yes	Revised CIB - Edition 10	Revised CIB - Edition 10	4/15/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	CMC Response to preliminary notice of potential review issues of NDA	CMC Response to preliminary notice of potential review issues of NDA. FDA comments were provided to Merck in the March 22, 2011 FDA letter which notified Merck that the Agency had filed the NDA for review.	4/28/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Patient Data Listings for Wirta site	Patient Data Listings for Dr. David Wirta's site to support FDA audit.	4/29/2011 0:00
2452		Safety	Safety Update Report (US Mktg App)	NDA	202-514		NA	Yes	Safety Update Report	Safety Update Report	5/6/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Response to 19Apr2011email requesting additional analysis in Studies 74458, 15-003 and 001	Response to 19Apr2011email requesting additional analysis in the Intent to Treat Population with LOCF and Per Protocol population Observed Cases in Studies 74458, 15-003 and 001 as well as datasets for the ISE included in the original NDA	5/11/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Clinical response regarding multiple investigator/site numbers	Clinical response to May 6, 2011 FDA request regarding the reason for multiple investigator/site numbers for the same Investigator.	5/24/2011 0:00
2452	SAFLUTAN	Marketing Application	Agency correspondence - Incoming	NDA	202-514		NA	No	FDA Queries: CMC	FDA Request for information: CMC (Analytical procedures, method validation results and batch analysis)	6/6/2011 0:00

2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	CMC Response to May 6, 2011 FDA Request	CMC Response to May 6, 2011 FDA Request for additional microbilogy and sterility information	6/8/2011 0:00
2452		Marketing Application	Marketing Application - Amendment to Pending	NDA	202-514		NA	Yes	TAFLUPROST (MK-2452) Request for Review of Proprietary Name	Country: US	6/9/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Clinical and Statistical Reponse to May 20, 2011 FDA Request	Clinical and Statistical Reponse to May 20, 2011 FDA Request. CMC questions in the May 20, 2011 request will be responded to in July.	6/10/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	CMC Response to June 6, 2011 FDA Request	CMC Response to June 6, 2011 FDA request reqarding missing sections which were original provided in Module 3 of the DMF for Asahi Glass Co., Ltd.	6/13/2011 0:00
2452	SAFLUTAN	Marketing Application	Agency correspondence (general) - Outgoing					No	FDA Queries: Clinical, CMC & Clin. Pharm	FDA request for information: clincal, CMC & Clin. Pharm	6/17/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Response to June 17th FDA Request for Clinical, Clin Pharm, and CMC information	Response to June 17th FDA Request for Clinical (Statistical Analysis), Clin Pharm, and CMC information. 42 new clinical tables are being included with this submission	6/30/2011 0:00
2452		Marketing Application	Marketing Application - Amendment to Pending	NDA	202-514		NA	Yes	Container Labels to support review of proposed tradename	Container Labels to support review of proposed tradename which was submitted for FDA review on June 9, 2011.	7/5/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Response to June 7, 2011 FDA Request for updated AE tables in Module 2	Response to June 7, 2011 FDA Request for updated AE tables in Module 2. BARDS provided response in Module 1.11.3 document	7/6/2011 0:00
2452	SAFLUTAN	Marketing Application	Marketing application - Original					No	E-mail from FDA Project Manager about endotoxin specification	E-mail from FDA Project Manager on Merck's response from April 28, 2011 regarding endotoxin specification	7/6/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	CMC Response to May 20th FDA Request	CMC Response to May 20th FDA Request; consists of Module 1.11.1, Module 2 and Module 3 documentation	7/11/2011 0:00
2452		Supp Marketing Appln	Response to Agency	NDA	202-514		NA	Yes	Tafluprost Ophthalmic Solution - Responses to July 19, 2011 Questions - US - Initial Filing		7/26/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	MK-02452 Tafluprost Opthalmic Solution - Responses to Questions - US Initial Filing		8/1/2011 0:00
2452	SAFLUTAN	Marketing Application	Agency correspondence - Incoming	NDA	202-514		NA	No	FDA Response to request for feedback	FDA response to Merck's question re data corrections due to minor audit findings at Dr. Wirta's site (PN001)	8/5/2011 0:00
2452	SAFLUTAN	Marketing Application	Marketing application - Original	NDA	202-514		NA	No	E-mail from FDA regarding interim specification for endotoxins.	E-mail from FDA stating that the Agency will consider an interim exdotoxin specification.	8/9/2011 0:00

2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Tafluprost (MK-2452) Response to FDA Request for Information	Reference is made to the New Drug Application cited above for tafluprost, submitted on January 7, 2011. Reference is also made to the August 4, 2011 e-mail communication from Mr. Althea Cuff, Regulatory Project Manager, FDA, to Dr. Chitkala Kalidas, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., (Merck), in which Ms. Cuff requested additional information regarding laminate pouch dimensions and materials as well as analytical validation studies discussed in the response submitted on July 26, 2011.	8/10/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Tafluprost Response to FDA request for pediatric waiver certification for NDA 202-514.	In accordance with FDCA Section 505B (a) (4)	8/12/2011 0:00
2452		IND/BBIND	Annual Report	IND	62,690	112		Yes	Ophthalmic Solution Annual Report for 30-Jun-2010 through 29-Jun-2011.		8/18/2011 0:00
2452	SAFLUTAN	Supp Marketing Appln	Response to Agency	NDA	202-514		NA	Yes	Tafluprost - Response to FDA Comments Regarding Endotoxin Testing	Complete response to the Agencyâ€™s request for an endotoxin specification to be included as part of the drug product specifications for the tafluprost NDA	8/22/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Tafluprost - Commitment to FDA to Provide 21 month Leachable Data		9/2/2011 0:00
2452	SAFLUTAN	Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Tafluprost - Response to FDA Questions Dated 29 Aug 2011 - Question #6 only		9/6/2011 0:00
2452	SAFLUTAN	Marketing Application	Agency correspondence - Incoming	NDA	202-514		NA	No	Tradename Approval Letter	Approval letter from DMEPA for tradename Zioptan	9/6/2011 0:00
2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	Tafluprost - Response to Agency Questions 1b, 2, 4 & 5 received August 29, 2011		9/13/2011 0:00
2452	SAFLUTAN	Marketing Application	Response to Agency	NDA	202-514		NA	Yes	ZIOPTAN (MK-2452) - Response to Agency Questions 1a, 1c, 1d and 3	Reference is made to the New Drug Application cited above for tafluprost, submitted on January 7, 2011. Reference is made to the FDA comments received from Mr. Constantine Markos, Regulatory Project Manager, FDA, on August 29, 2011. Reference is made to the response submitted by Merck on September 6, 2011 to Question #6 received on August 29, 2011. Reference is also made to the response submitted by Merck on September 13, 2011 to Questions #1b, #2, #4 and #5 on August 29, 2011. With this submission, Merck Sharp and Dohme Corp., a subsidiary of Merck and Co., Inc., (Merck), is submitting Section 1.11.1 â€“ Quality Information Amendment â€“ Response to Agency Questions 1a, 1c, 1d and 3, received on August 29, 2011.	9/27/2011 0:00

2452	SAFLUTAN	Marketing Application	Agency correspondence - Incoming	NDA	202-514		NA	No	CMC information request	Request from Ms. Althea Cuff, Office of New Drugs Quality Assessment regarding primary container and analytical validation studies.	9/27/2011 0:00
2452	SAFLUTAN	Marketing Application	Response to Agency					Yes	ZIOPTAN (Tafluprost) Response to FDA for Information on Cetero Research	Reference is made to the FDA communication dated September 29, 2011 in reference to NDA 202-514, informing Sponsors of significant violations by Cetero Research in Houston, Texas and requesting information regarding any studies submitted to the aforementioned NDA that were conducted by Cetero during the period of April 1, 2005 to June 15, 2010. This correspondence is to inform you that our Drug Metabolism and Quality Assurance groups are aware of the issue with Cetero. It has been confirmed that the aforementioned NDA does not contain any clinical studies or non-clinical studies conducted by Cetero during the time period of concern.	10/13/2011 0:00
2452	SAFLUTAN	Marketing Application	Marketing application - Original	IND	62,690	NA		No	Media fill procedures not adequate.	Media fill issues inadequate - request from FDA to amend.	10/18/2011 0:00
2452	SAFLUTAN	Marketing Application	Response to Agency	NDA	202-514		NA	Yes	ZIOPTAN (MK-2452) Response to FDA comments regarding proposed Prescribing Information	Reference is made to the New Drug Application cited above for ZIOPTAN, submitted on January 7, 2011. Reference is made to the FDA labeling comments received from Mr. Constantine Markos, Regulatory Project Manager, FDA, on October 17, 2011 regarding the proposed Prescribing Information (PI). With this submission, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., (Merck), is submitting the labeling responses for ZIOPTAN. This includes annotated, clean and track changes versions of the Prescribing Information (PI) and Patient Product Insert (PPI), respectively (6 PDF files). In addition, clean and track changes versions of the PI and PPI, respectively, are also being submitted as MS Word files for use by the Agency for editing purposes (4 MS Word files). Also included is a proposal to retain the PPI for ZIOPTAN.	10/26/2011 0:00

2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	ZIOPTAN (MK-2452) Response to Agency Questions Regarding Media Fill Procedures	With this submission, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., (Merck), is submitting a response document and updated Module 3 Section 3.2.P.3.5 for ZIOPTAN.With this submission, Merck is providing our response to the 3 points required for resolution of the identified media fill issue. As you will note in our response we have confirmed that tafluprost is using a single filling line, we have committed to amend the media fill procedures and confirm that no additional media fill challenges will be performed until the updated SOP is implemented. Lastly, we commit to perform and submit the results of another media fill in the near future using the amended procedure.In addition to our response, we are providing a revised CTD Module 3 Section 3.2.P.3.5. that has been updated to reflect the changes being implemented in our media fill procedures	10/27/2011 0:00
2452	SAFLUTAN	Marketing Application	Response to Agency	NDA	202-514		NA	Yes	ZIOPTAN (MK-2452) Updated Establishment Information for Unither		11/2/2011 0:00
2452	SAFLUTAN	Marketing Application	Response to Agency	NDA	202-514		NA	Yes	ZIOPTAN (MK-2452) Merck Commitment to Submit Media Fill Data	Reference is made to the New Drug Application cited above for tafluprost, submitted on January 7, 2011. Reference is made to the October 27, 2011 teleconference between Merck and the FDA during which Dr. Wiley Chambers, Supervisory Medical Officer, Division of Transplant & Ophthalmology Products, FDA, stated that the Agency is willing to accept the latest response from Merck on Media Fill runs (submitted via e-mail on Oct 26, 2011) with the exception that instead of the 1 media fill run under the new SOP, the Agency would require Merck to submit data from 3 consecutive media fill runs by the end of 1Q2012.	11/2/2011 0:00

2452	SAFLUTAN	Marketing Application	Response to Agency	NDA	202-514		NA	Yes	ZIOPTAN (MK-2452) Response to Agency Updated Prescribing Information	With this submission, Merck is providing our response to the comments received from the Agency on the Prescribing Information (PI) for ZIOPTAN during the teleconference on November 1st, 2011. These documents include the same information that was previously submitted to the FDA in the e-mail from Dr. Chitkala Kalidas, Merck, to Ms. Judit Milstein, Supervisory Consumer Safety Officer, FDA, and Mr. Constantine Markos, Regulatory Health Project Manager, FDA, on November 2, 2011, with the exception of one erroneous spelling for an inactive ingredient that has been corrected from sodium dihydrogen phosphate dehydrate to sodium dihydrogen phosphate dihydrate in this submission that was not previously corrected in the version of the PI submitted to the FDA on November 2, 2011.	11/3/2011 0:00
2452	SAFLUTAN	Marketing Application	Response to Agency	NDA	202-514		5459	Yes	ZIOPTAN (MK02452) - Response to Agency Carton and Container Labels		11/4/2011 0:00
2452	SAFLUTAN	Marketing Application	Agency correspondence - Incoming	NDA	202-514		NA	No	Complete Response Letter	Complete response letter received from FDA for Zioptan.	11/7/2011 0:00
2452		Marketing Application	Agency correspondence (general) - Outgoing	NDA	202-514		NA	Yes	ZIOPTAN (MK-2452) Request for Agency Feedback	Reference is made to the New Drug Application cited above for ZIOPTAN, submitted on January 7, 2011. Reference is also made to the complete response letter received on November 7th, 2011 citing additional information needed on final drug product stability and a safety update. Final reference is made to the telephone conversation between Ms. Judit Milstein, Supervisory Project Manager, FDA and Dr. Chitkala Kalidas, Merck, on November 30, 2011, regarding the expiry date for tafluprost during which Ms. Milstein requested Dr. Kalidas to submit Merck's request for Agency feedback on the expiry date in the form of a letter to the FDA, along with the rationale for this request.	12/5/2011 0:00
2452		Marketing Application	Agency correspondence (general) - Outgoing	NDA	202-514		NA	Yes	ZIOPTAN (MK-2452) Request for Agency Feedback on Safety Update Report		12/7/2011 0:00

2452		Marketing Application	Response to Agency	NDA	202-514		NA	Yes	ZIOPTAN (MK-2452) - Re-submission (Response to Complete Response Letter For NDA 202514)	This is a re-submission to provide Merck's response to the Complete Response Letter received from the FDA on November 7, 2011 for NDA 202514. Merck considers this to be a complete response to the deficiencies outlined in the Complete Response Letter cited above for NDA 202514. With this re-submission for NDA 202514, Merck requests FDA approval of ZIOPTAN â€œfor the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertensionâ€. Reference is made to the New Drug Application cited above for ZIOPTAN, submitted on January 7, 2011. Reference is also made to the IND 62, 690 originally submitted to the FDA on May 23, 2011 by Santen Inc., and transferred to Merck on November 12, 2009.	1/13/2012 0:00
2452	SAFLUTAN	Supp Marketing Appln	Supplemental marketing application - Labeling - Other	NDA	202-514		NA	Yes	ZIOPTAN - Update to proposed USPI for consistency with COSOPT PF USPI		1/23/2012 0:00
2452	ZIOPTAN	Marketing Application	NDA Approval Letter	NDA	202-514		NA	No	Approval letter from FDA for ZIOPTAN NDA	Formal Letter from FDA approving the NDA for ZIOPTAN	2/10/2012
2452	ZIOPTAN	Marketing Application	Final Printed Label	NDA	202-514		NA	No	SPL for eList - NDA 202-514, original NDA approval, ZIOPTAN circular 6073102	This submission provides the SPL for eList for ZIOPTAN and corresponds to content of labeling for original NDA approval received 10-Feb-2012	2/16/2012 0:00

NA = not availab le

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 2

Patent #: 5886035 **Issue Dt:** 03/23/1999 **Application #:** 08993017 **Filing Dt:** 12/18/1997

Inventors: EIICHI SHIRASAWA, MASAAKI KAGEYAMA, TADASHI NAKAJIMA, TAKASHI NAKANO, NOBUAKI MORI et al

Title: DIFLUOROPROSTAGLANDIN DERIVATIVES AND THEIR USE

Assignment: 1

Reel/Frame: 008954/0860 **Recorded:** 12/18/1997 **Pages:** 3

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors:

SHIRASAWA, EIICHI	**Exec Dt:** 12/05/1997
KAGEYAMA, MASAAKI	**Exec Dt:** 12/05/1997
NAKAJIMA, TADASHI	**Exec Dt:** 12/05/1997
NAKANO, TAKASHI	**Exec Dt:** 11/28/1997
MORI, NOBUAKI	**Exec Dt:** 11/28/1997
SASAKURA, HIDESHI	**Exec Dt:** 12/01/1997
MATSUMURA, YASUSHI	**Exec Dt:** 12/01/1997
MORIZAWA, YOSHITOMI	**Exec Dt:** 11/28/1997

Assignees: ASAHI GLASS COMPANY LTD.
1-2 MARUNOUCHI 2-CHOME, CHIYODA-KU
TOKYO 100, JAPAN
SANTEN PHARMACEUTICAL CO., LTD.
9-19, SHIMOSHINJO 3-CHOME,HIGASHIYODOGAWA-KU
OSAKA-SHI, OSAKA, JAPAN

Correspondent: OBLON, SPIVAK, MCCLELLAND, ET AL.
NORMAN F. OBLON
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VA 22202

Assignment: 2

Reel/Frame: 010557/0067 **Recorded:** 02/18/2000 **Pages:** 11

Conveyance: CHANGE OF CORPORATE ADDRESS

Assignor: ASAHI GLASS COMPANY LTD. **Exec Dt:** 12/13/1999

Assignee: ASAHI GLASS COMPANY LTD.
12-1, YURAKUCHO 1-CHOME CHIYODA-KU
TOKYO, JAPAN

Correspondent: OBLON, SPIVAK, MCCLELLAND, MAIER ET AL
MARVIN J. SPIVAK
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202

Search Results as of: 03/09/2012 01:30 PM

If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350. v.2.3.1
Web interface last modified: Jan 26, 2012 v.2.3.1

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 202514

NDA APPROVAL

Merck Sharp & Dohme Corp.
Attention: Chitkala Kalidas, Ph.D.
Director, Worldwide Regulatory Affairs
P.O. Box 2000, RY33-204
Rahway, New Jersey 07065-0900

Dear Dr. Kalidas:

Please refer to your New Drug Application (NDA) dated and received January 7, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ZIOPTAN (tafluprost ophthalmic solution) 0.0015%.

We acknowledge receipt of your amendments dated:

January 7, 2011 (2)	January 10, 2011	January 14, 2011
January 20, 2011	February 9, 2011	February 17, 2011
February 28, 2011	March 23, 2011	March 29, 2011
April 4, 2011	April 6, 2011	April 28, 2011
April 29, 2011	May 6, 2011	May 11, 2011
May 24, 2011	June 8, 2011	June 9, 2011
June 10, 2011	June 13, 2011	June 30, 2011
July 5, 2011	July 6, 2011	July 11, 2011
July 26, 2011	August 1, 2011	August 4, 2011
August 10, 2011	August 12, 2011	August 22, 2011
September 2, 2011	September 6, 2011	September 13, 2011
September 27, 2011	October 13, 2011	October 26, 2011
October 27, 2011	November 2, 2011 (2)	November 3, 2011
November 7, 2011	December 6, 2011	December 7, 2011
January 13, 2012	January 23, 2012	

The January 13, 2012, submission constituted a complete response to our November 7, 2011, action letter.

This new drug application provides for the use of ZIOPTAN (tafluprost ophthalmic solution) for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert and patient package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton, container and pouch labels that are identical to the enclosed carton, container and pouch labels submitted on November 4, 2011, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton, Container and Pouch Labels for approved NDA 202514**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an un-approved new drug.

Your application for ZIOPTAN was not referred to an FDA advisory committee because it is a member of the class of ophthalmic prostaglandin analogs with similar potential risks and benefits as other members in this class. The benefits and risks of using prostaglandin analogs to treat elevated intraocular pressure have been previously discussed at a meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee on December 8, 1995, and the safety profile of tafluprost did not raise any new significant safety issues. The clinical study design was similar to other approved drugs in this class and we are not aware of any controversial issues that would benefit from further advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or in-applicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable as there are too few children with this disease/condition to study.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Health Project Manager for this application.

If you have any questions, please call Constantine J. Markos, B.S., Pharm.D., R.Ph., Regulatory Health Project Manager, at (301) 796-3871.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S): Content of Labeling (Package Insert and Patient Package Insert)
Carton, Container and Pouch Labels

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZIOPTAN (tafluprost ophthalmic solution) 0.0015% safely and effectively. See full prescribing information for ZIOPTAN.

ZIOPTAN™ (tafluprost ophthalmic solution) 0.0015%
Initial U.S. Approval: 2012

----------INDICATIONS AND USAGE----------

- ZIOPTAN (tafluprost ophthalmic solution) 0.0015% is a prostaglandin analog indicated for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

---------- DOSAGE AND ADMINISTRATION----------

- One drop in the affected eye(s) once daily in the evening. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Ophthalmic solution containing tafluprost 0.015 mg/mL. (3)

----------CONTRAINDICATIONS ----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Pigmentation

Pigmentation of the iris, periorbital tissue (eyelid) and eyelashes can occur. Iris pigmentation is likely to be permanent. (5.1)

- Eyelash Changes

Gradual changes to eyelashes including increased length, thickness and number of lashes. Usually reversible. (5.2)

---------- ADVERSE REACTIONS----------

- Most common ocular adverse reaction is conjunctival hyperemia (range 4% – 20%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

- Use in pediatric patients is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: XX/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Pigmentation
5.2 Eyelash Changes
5.3 Intraocular Inflammation
5.4 Macular Edema
6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
6.2 Postmarketing Experience
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Nightly Application
17.2 Handling the Single-Use Container
17.3 Potential for Pigmentation
17.4 Potential for Eyelash Changes
17.5 When to Seek Physician Advice
17.6 Use with Other Ophthalmic Drugs
17.7 Storage Information

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZIOPTAN™ (tafluprost ophthalmic solution) 0.0015% is indicated for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

The recommended dose is one drop of ZIOPTAN in the conjunctival sac of the affected eye(s) once daily in the evening.

The dose should not exceed once daily since it has been shown that more frequent administration of prostaglandin analogs may lessen the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 2 to 4 hours after the first administration with the maximum effect reached after 12 hours.

ZIOPTAN may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is being used, each one should be administered at least 5 minutes apart.

The solution from one individual unit is to be used immediately after opening for administration to one or both eyes. Since sterility cannot be maintained after the individual unit is opened, the remaining contents should be discarded immediately after administration.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing tafluprost 0.015 mg/mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

Tafluprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as tafluprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of tafluprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with ZIOPTAN can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly. *[See Patient Counseling Information (17.3).]*

5.2 Eyelash Changes

ZIOPTAN may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, color, thickness, shape and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

ZIOPTAN should be used with caution in patients with active intraocular inflammation (e.g., iritis/uveitis) because the inflammation may be exacerbated.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin F2α analogs. ZIOPTAN should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Preservative-containing or preservative-free tafluprost 0.0015% was evaluated in 905 patients in five controlled clinical studies of up to 24-months duration. The most common adverse reaction observed in patients treated with tafluprost was conjunctival hyperemia which was reported in a range of 4% – 20% of patients. Approximately 1% of patients discontinued therapy due to ocular adverse reactions.

Ocular adverse reactions reported at an incidence of ≥2% in these clinical studies included ocular stinging/irritation (7%), ocular pruritus including allergic conjunctivitis (5%), cataract (3%), dry eye (3%), ocular pain (3%), eyelash darkening (2%), growth of eyelashes (2%) and vision blurred (2%).

Nonocular adverse reactions reported at an incidence of 2% – 6% in these clinical studies in patients treated with tafluprost 0.0015% were headache (6%), common cold (4%), cough (3%) and urinary tract infection (2%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of tafluprost. Because postapproval adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Teratogenic effects: In embryo-fetal development studies in rats and rabbits, tafluprost administered intravenously was teratogenic. Tafluprost caused increases in post-implantation losses in rats and rabbits and reductions in fetal body weights in rats. Tafluprost also increased the incidence of vertebral skeletal abnormalities in rats and the incidence of skull, brain and spine malformations in rabbits. In rats, there were no adverse effects on embryo-fetal development at a dose of 3 µg/kg/day corresponding to maternal plasma levels of tafluprost acid that were 343-times the maximum clinical exposure based on C_{max}. In rabbits, effects were seen at a tafluprost dose of 0.03 µg/kg/day corresponding to maternal plasma levels of tafluprost acid during organogenesis that were approximately

5 times higher than the clinical exposure based on C_{max}. At the no-effect dose in rabbits (0.01 µg/kg/day), maternal plasma levels of tafluprost acid were below the lower level of quantification (20 pg/mL).

In a pre- and postnatal development study in rats, increased mortality of newborns, decreased body weights and delayed pinna unfolding were observed in offsprings. The no observed adverse effect level was at a tafluprost intravenous dose of 0.3 µg/kg/day which is greater than 3 times the maximum recommended clinical dose based on body surface area comparison.

There are no adequate and well-controlled studies in pregnant woman. Although animal reproduction studies are not always predictive of human response, ZIOPTAN should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Women of childbearing age/potential should have adequate contraceptive measures in place.

8.3 Nursing Mothers

A study in lactating rats demonstrated that radio-labeled tafluprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZIOPTAN is administered to a nursing woman.

8.4 Pediatric Use

Use in pediatric patients is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

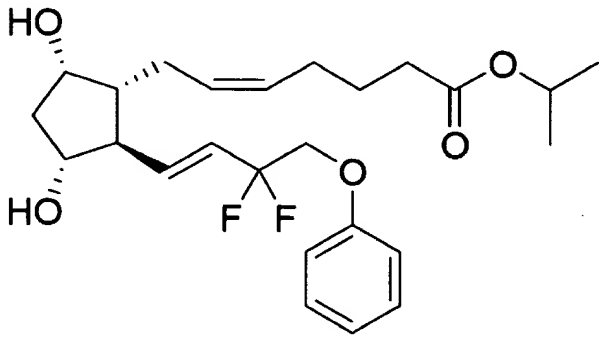
8.5 Geriatric Use

No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

11 DESCRIPTION

Tafluprost is a fluorinated analog of prostaglandin F2α. The chemical name for tafluprost is 1-methylethyl (*5Z*)-7-{(*1R, 2R, 3R, 5S*)-2-[(*1E*)-3,3-difluoro-4-phenoxy-1-butenyl}-3,5-dihydroxycyclopentyl]-5-heptenoate. The molecular formula of tafluprost is $C_{25}H_{34}F_2O_5$ and its molecular weight is 452.53.

Its structural formula is:



Tafluprost is a colorless to light yellow viscous liquid that is practically insoluble in water.

ZIOPTAN (tafluprost ophthalmic solution) 0.0015% is supplied as a sterile solution of tafluprost with a pH range of 5.5 - 6.7 and an Osmolality range of 260 – 300 mOsmol/kg.

ZIOPTAN contains Active: tafluprost 0.015 mg/mL; Inactives: glycerol, sodium dihydrogen phosphate dihydrate, disodium edetate, polysorbate 80, hydrochloric acid and/or sodium hydroxide (to adjust pH) and Water for Injection.

ZIOPTAN does not contain a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tafluprost acid, a prostaglandin analog is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow. The exact mechanism of action is unknown at this time.

12.3 Pharmacokinetics

Absorption

Following instillation, tafluprost is absorbed through the cornea and is hydrolyzed to the biologically active acid metabolite, tafluprost acid. Following instillation of one drop of the 0.0015% solution once daily into each eye of healthy volunteers, the plasma concentrations of tafluprost acid peaked at a median time of 10 minutes on both Days 1 and 8. The mean plasma C_{max} of tafluprost acid were 26 pg/mL and 27 pg/mL on Day 1, and Day 8, respectively. The mean plasma AUC estimates of tafluprost acid were 394 pg*min/mL and 432 pg*min/mL on Day 1 and 8, respectively.

Metabolism

Tafluprost, an ester prodrug, is hydrolyzed to its biologically active acid metabolite in the eye. The acid metabolite is further metabolized via fatty acid β-oxidation and phase II conjugation.

Elimination

Mean plasma tafluprost acid concentrations were below the limit of quantification of the bioanalytical assay (10 pg/mL) at 30 minutes following topical ocular administration of tafluprost 0.0015% ophthalmic solution.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Tafluprost was not carcinogenic when administered subcutaneously daily for 24 months at doses up to 30 µg/kg/day in rats and for 18 months at doses up to 100 µg/kg/day in mice (over 1600- and 1300-times, respectively, the maximum clinical exposure based on plasma AUC).

Tafluprost was not mutagenic or clastogenic in a battery of genetic toxicology studies, including an *in vitro* microbial mutagenesis assay, an *in vitro* chromosomal aberration assay in Chinese hamster lung cells, and an *in vivo* mouse micronucleus assay in bone marrow.

In rats, no adverse effects on mating performance or fertility were observed with intravenous dosing of tafluprost at a dose of 100 µg/kg/day (over 14000- times the maximum clinical exposure based on plasma C_{max} or over 3600- times based on plasma AUC).

14 CLINICAL STUDIES

In clinical studies up to 24 months in duration, patients with open-angle glaucoma or ocular hypertension and baseline pressure of 23 - 26 mm Hg who were treated with ZIOPTAN dosed once daily in the evening demonstrated reductions in intraocular pressure at 3 and 6 months of 6 – 8 mmHg and 5 – 8 mmHg, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZIOPTAN (tafluprost ophthalmic solution) 0.0015% is supplied as a sterile solution in translucent low density polyethylene single-use containers packaged in foil pouches (10 single-use containers per pouch). Each single-use container has 0.3 mL solution corresponding to 0.0045 mg tafluprost.

NDC 0006-3931-30; Unit-of-Use Carton of 30.
NDC 0006-3931-54; Unit-of-Use Carton of 90.

Storage:

Store refrigerated at 2-8°C (36-46°F). Store in the original pouch. After the pouch is opened, the single-use containers may be stored in the opened foil pouch for up to 28 days at room temperature: 20-25°C (68-77°F). Protect from moisture. Write down the date you open the foil pouch in the space provided on the pouch. Discard any unused containers 28 days after first opening the pouch.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

17.1 Nightly Application

Patients should be advised to not exceed once daily dosing since more frequent administration may decrease the intraocular pressure lowering effect of ZIOPTAN.

17.2 Handling the Single-Use Container

Patients should be advised that ZIOPTAN is a sterile solution that does not contain a preservative. The solution from one individual unit is to be used immediately after opening for administration to one or both eyes. Since sterility cannot be maintained after the individual unit is opened, the remaining contents should be discarded immediately after administration.

17.3 Potential for Pigmentation

Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of ZIOPTAN.

17.4 Potential for Eyelash Changes

Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with ZIOPTAN. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

17.5 When to Seek Physician Advice

Patients should be advised that if they develop a new ocular condition (e.g., trauma or infection), experience a sudden decrease in visual acuity, have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of ZIOPTAN.

17.6 Use with Other Ophthalmic Drugs

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

17.7 Storage Information

Patients should be instructed on proper storage of cartons, unopened foil pouches, and opened foil pouches *[see How Supplied/Storage and Handling (16)]*. Recommended storage for cartons and unopened foil pouches is to store refrigerated at 2-8°C (36-46°F). After the pouch is opened, the single-use containers may be stored in the opened foil pouch for up to 28 days at room temperature: 20-25°C (68-77°F). Protect from moisture.

Rx Only

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:
Laboratoire Unither
ZI de la Guerie
F-50211 COUTANCES Cedex
France

US Patent No.: 5,886,035

Revised: XX/2012

6073101

PATIENT INFORMATION
ZIOPTAN™ (zye OP tan)
(tafluprost ophthalmic solution) 0.0015%

Read this Patient Information before you start using ZIOPTAN™ and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is ZIOPTAN?

ZIOPTAN is a prescription sterile eye drop solution. ZIOPTAN is used to lower the pressure in the eye (intraocular pressure) in people with open-angle glaucoma or ocular hypertension when their eye pressure is too high. ZIOPTAN belongs to a group of medicines called prostaglandin analogs.

ZIOPTAN is not for use in children.

What should I tell my doctor before using ZIOPTAN?

Before you use ZIOPTAN, tell your doctor if you:

- have or have had eye problems including any surgery on your eye or eyes
- are using any other eye medicines
- have any other medical problems
- are pregnant or plan to become pregnant. It is not known if ZIOPTAN will harm your unborn baby. You should use an effective method of birth control while you use ZIOPTAN. If you become pregnant while using ZIOPTAN talk to your doctor right away.
- are breastfeeding or plan to breastfeed. It is not known if ZIOPTAN passes into your breast milk. Talk to your doctor about the best way to feed your baby if you use ZIOPTAN.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take ZIOPTAN?

Read the Instructions for Use at the end of this Patient Information leaflet for additional instructions about the right way to use ZIOPTAN.

- **Use 1 drop of ZIOPTAN in your eye (or eyes) each evening.** Talk to your doctor or pharmacist if you are not sure how to use ZIOPTAN.
- Your ZIOPTAN may not work as well if you use it more than 1 time each evening.
- If you use other medicines in your eye, wait at least 5 minutes between using ZIOPTAN and your other eye medicines.
- Use your ZIOPTAN right away after opening. Each ZIOPTAN single-use container is sterile and is to be used 1 time then thrown away. Do not save any ZIOPTAN that may be left over after you use your medicine. Using ZIOPTAN that is not sterile may cause other eye problems.

What are the possible side effects of ZIOPTAN?

ZIOPTAN may cause serious side effects including:

- **changes in the color of your eye (iris).** Your iris may become more brown in color while using ZIOPTAN. This color change may not go away when you stop using ZIOPTAN. If ZIOPTAN is used in 1 eye only, the color of that eye may always be a different color from the color of your other eye.
- **darkening of the color of the skin around your eye (eyelid).** These skin changes usually go away when you stop using ZIOPTAN.
- **increasing the length, thickness, color, or number of your eyelashes.** These eyelash changes usually go away when you stop using ZIOPTAN.
- **hair growth on your eyelids.** This hair growth usually goes away when you stop using ZIOPTAN.

The most common side effects of ZIOPTAN include:

- redness, stinging or itching of your eye
- cataract formation
- dry eye
- eye pain
- blurred vision
- headache
- common cold
- cough
- urinary tract infection

Tell your doctor if you have any new eye problems while using ZIOPTAN including:

- an eye injury
- an eye infection
- a sudden loss of vision
- eye surgery
- swelling and redness of and around your eye (conjunctivitis)
- problems with your eyelids

Tell your doctor if you have any other side effects that bother you.

These are not all the possible side effects of ZIOPTAN. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZIOPTAN?

Keep the foil pouches and ZIOPTAN single-use containers dry.

Before opening the foil pouches:

- Store the unopened foil pouches in a refrigerator between 36°F to 46°F (2°C to 8°C).
- Do not open the pouch containing ZIOPTAN until you are ready to use the eye drops.

After opening the foil pouch:

- Store the opened foil pouch at room temperature, between 68°F to 77°F (20°C to 25°C), for up to 28 days.
- Throw away all unused ZIOPTAN single-use containers in the opened foil pouch after 28 days.
- Keep the ZIOPTAN single-use containers in their original foil pouch.
- After opening the foil pouch, refrigeration is not required.

Keep ZIOPTAN and all medicines out of the reach of children.

General information about the safe and effective use of ZIOPTAN.

Do not use ZIOPTAN for a condition for which it was not prescribed. Do not give ZIOPTAN to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about ZIOPTAN. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ZIOPTAN that is written for health professionals.

What are the ingredients in ZIOPTAN?

Active ingredients: tafluprost

Inactive ingredients: glycerol, sodium dihydrogen phosphate dihydrate, disodium edetate, and polysorbate 80, hydrochloric acid and/or sodium hydroxide, and water

Instructions for Use

Read these Instructions for Use before using your ZIOPTAN and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

Important:

- **ZIOPTAN is for the eye only. Do not swallow ZIOPTAN.**
- ZIOPTAN single-use containers are packaged in a foil pouch.
- **Do not** use the ZIOPTAN single-use containers if the foil pouch is opened.
- Write down the date you open the foil pouch in the space provided on the pouch.

Every time you use ZIOPTAN:

Step 1. Wash your hands.	
Step 2. Take the strip of single-use containers from the foil pouch.	
Step 3. Pull off one single-use container from the strip.	

Step 4. Put the remaining strip of single-use containers back in the foil pouch and fold the edge to close the pouch.	
Step 5. Hold the single-use container upright. Make sure that your ZIOPTAN medicine is in the bottom part of the single-use container. **See Figure A.**	 **Figure A**
Step 6. Open the single-use container by twisting off the tab. **See Figure B.**	 **Figure B**
Step 7. Tilt your head backwards. If you are unable to tilt your head, lie down. **Step 8.** Place the tip of the single-use container close to your eye. Be careful not to touch your eye with the tip of the single-use container. **See Figure C.**	 **Figure C**
Step 9. Pull your lower eyelid downwards and look up. **Step 10.** Gently squeeze the container and let 1 drop of ZIOPTAN fall into the space between your lower eyelid and your eye. If a drop misses your eye, try again. **See Figure D.**	 **Figure D**

- If your doctor has told you to use ZIOPTAN drops in both eyes, repeat Steps 7 to 10 for your other eye.

- There is enough ZIOPTAN in one single-use container for both of your eyes.
- **Throw away the opened single-use container with any remaining ZIOPTAN right away.**

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Rx only


Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:
Laboratoire Unither
ZI de la Guerie
F-50211 COUTANCES Cedex
France

US Patent No.: 5,886,035

Revised: XX/2012

6073101

Professional Sample–
Not For Retail Sale

For Topical Application in the Eye

STORAGE:
Store refrigerated at 2-8°C (36-46°F). Store in original pouch. After the pouch is opened, the single-use containers may be stored in the opened foil pouch for up to 28 days at room temperature: 20-25°C (68-77°F).
Protect from moisture.

USUAL DOSAGE:
One drop in the affected eye(s) once daily in the evening. The solution from one single-use container is to be used immediately after opening for administration to one or both eyes.

ATTENTION:
Use the eye drops immediately after opening the container. Discard the opened container with any remaining contents immediately after use.

Manuf. for:
Merck Sharp & Dohme Corp.,
a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

By: Laboratoire Unither
ZI de la Guerie
F-50211 COUTANCES Cedex
France
Tafluprost (active ingred.) Made in Japan
Formulated in France

N 3 0006-3931-36 6

6062802 SRN 7650

ZIOPTAN™ (tafluprost ophthalmic solution) 0.0015% For Topical Application in the Eye

6062802
1SAFL2561US

Professional Sample–
Not For Retail Sale

ZIOPTAN™
(tafluprost ophthalmic solution)
0.0015%

For Topical Application in the Eye

REFRIGERATE (2-8°C or 36-46°F)

Single-Use Containers
Preservative-Free, Sterile

Contains:
Active: tafluprost 0.0015%
(4.5 mcg per single-use container)
Inactive ingredients: glycerol, sodium dihydrogen phosphate dihydrate, disodium edetate, polysorbate 80, Water for Injection. Hydrochloric acid and/or sodium hydroxide are added to adjust pH.

Rx only
10 Single-Use Containers:
1 pouch x 10 single-use containers
(0.3 mL each)

Lot
Exp.

ZIOPTAN™ (tafluprost ophthalmic solution) 0.0015% For Topical Application in the Eye

66ETU2561/E

Store refrigerated at 2-8 °C (36-46 °F). Store in original pouch.
After the pouch is opened, the single-use containers may be stored in the opened foil pouch for up to 28 days at room temperature: 20-25°C (68 - 77°F).
Protect from moisture.

USUAL DOSAGE:
One drop in the affected eye(s) once daily in the evening. The solution from one single-use container is to be used immediately after opening for administration to one or both eyes.

ATTENTION:
Use the eye drops immediately after opening the container. Discard the opened container with any remaining contents immediately after use.

Manuf. for
Merck Sharp & Dohme Corp.,
a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

By: Laboratoire Unither
21 de la Guerie
F-50211 COUTANCES Cedex
France
Tafluprost (active ingred.) Made in Japan
Formulated in France

3 0006-3931-30 4

For Topical Application in the Eye

'TAN™
ɔrost ophthalmic solution) 0.0015%

6010903
1SAFL2560US

For Topical Application in the Eye

'TAN™
ɔrost ophthalmic solution) 0.0015%

(tafluprost ophthalmic solution)
0.0015%

For Topical Application in the Eye

REFRIGERATE (2-8°C or 36-46°F)

Single-Use Containers
Preservative-Free, Sterile

Contains:
Active: tafluprost 0.0015%
(4.5 mcg per single-use container)
Inactive ingredients: glycerol, sodium dihydrogen phosphate dihydrate, disodium edetate, polysorbate 80, Water for Injection. Hydrochloric acid and/or sodium hydroxide are added to adjust pH.

Rx only
30 Single-Use Containers:
3 pouches x 10 single-use containers
(0.3 mL each)

6010903

Lot
Exp.

66ETU2560/B

Use the eye drops immediately after opening the container. Discard the opened container with any remaining contents immediately after use.

Manuf. for:
Merck Sharp & Dohme Corp.,
a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

By: Laboratoire Unither
ZI de la Guerie
F-50211 COUTANCES Cedex
France
Tafluprost (active ingred.) Made in Japan
Formulated in France

3 0006-3931-54 0

(solution)

6011003
1SAFL2562US

For Topical Application in the Eye

REFRIGERATE (2-8°C or 36-46°F)

Single-Use Containers
Preservative-Free, Sterile

Contains:
Active: tafluprost 0.0015%
(4.5 mcg per single-use container)
Inactive ingredients: glycerol, sodium dihydrogen phosphate dihydrate, disodium edetate, polysorbate 80, Water for Injection. Hydrochloric acid and/or sodium hydroxide are added to adjust pH.

Rx only
90 Single-Use Containers:
9 pouches x 10 single-use containers
(0.3 mL each)

6011003

Lot
Exp.

66ETU2562/B

For Topical Application in the Eye

0.0015%

NDC 0006-3931-10

ZIOPTAN™

(tafluprost ophthalmic solution) 0.0015%

For Topical Application in the Eye

Single-Use Containers

Preservative-Free, Sterile

Contains: Active: tafluprost 0.0015%
(4.5 mcg per single-use container)
Inactive ingredients: glycerol, sodium dihydrogen phosphate dihydrate, disodium edetate, polysorbate 80, Water for Injection. Hydrochloric acid and/or sodium hydroxide are added to adjust pH.

STORAGE: Store refrigerated at 2-8°C (36-46°F). Store in original pouch. After the pouch is opened, the single-use containers may be stored in the opened foil pouch for up to 28 days at room temperature: 20-25°C (68-77°F). Protect from moisture.

Write down the date the pouch is opened here: _____

USUAL DOSAGE: One drop in the affected eye(s) once daily in the evening. The solution from one single-use container is to be used immediately after opening for administration to one or both eyes.

ATTENTION: Use the eye drops immediately after opening the container. Discard the opened container with any remaining contents immediately after use.

Manuf. for: Merck Sharp & Dohme Corp.,
a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA
By: Laboratoire Unither
ZI de la Guerie
F-50211 COUTANCES Cedex, France
Tafluprost (active ingred.) Made in Japan
Formulated in France

0006-3931-10

Lot

Exp.

Rx only

6011103

10 Single-Use Containers (0.3 mL each)

62COM2560/B

3931/1SAR2560US/1SAR2562US

62COM2560/B

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDWARD M COX
02/10/2012